AMERICAN JOURNAL

OF

DISEASES OF CHILDREN

VOLUME 21

1921

CONTENTS OF VOLUME 21

THE FOOD REQUIREMENTS OF CHILDREN

I. TOTAL CALORIC REQUIREMENTS *

L. EMMETT HOLT, M.D., and HELEN L. FALES

NEW YORK

In the course of our metabolism observations on young children many interesting facts have been brought out with respect to the general food requirements as to total calories, distribution of the calories as fat, carbohydrate and protein, and other factors in the diet which must be considered. One notes in the literature on the food requirements of growing children a great difference of opinion among the various observers who have studied the subject. Many writers have taken up this problem from only a single point of view, such as the total caloric requirement, or the basal requirement, or the food needs in respect to one or another of the accessory food substances, the so-called "vitamins."

We have, therefore, thought it desirable to consider in its different aspects the whole subject of the food requirements of the child during the entire period of growth.

We shall discuss in this paper the total caloric requirements of children and the different factors which must be reckoned with in estimating the total calories. In succeeding papers we shall take up the proper distribution of the calories of the food as fat, carbohydrate and protein, also other important factors in the diet such as roughage, the difference in growth-promoting properties of the different proteins, the supply of essential inorganic salts and the accessory food substances or vitamins.

At various times and by various authors each of the different factors mentioned has been discussed, but as yet no one has attempted to correlate them all and study the food needs of the child in the entire aspect. The estimates of total caloric requirements of children made by some authors have been purely hypothetical, while others have been based on the requirements of adults.

Observations made during the last few years, especially in this country, have thrown new light on the question of the total calories

needed by the growing child. It is essential to review not only this published work, but also most of the older observations, made chiefly in Germany. From these older observations conclusions have been drawn which do not seem to be warranted either by the number of children studied or the conditions under which they lived. For instance, one author made but a single observation on one child; another's observations were made almost entirely on his own children; those of a third were made on a considerable group of young children who were inmates of an orphan asylum, most of whom were very much under weight; a fourth studied three girls, two of whom were very much over weight.

It is recognized by all who have studied this subject that even in normal healthy children there are very considerable individual variations in food requirements. These variations are certainly much greater in abnormal children or in those studied under unusual conditions. Yet the small number of observations made by some of the German authors referred to are quoted over and over again in textbooks and periodical literature and have been made the basis of very broad and widely accepted deductions. In the light of more recent studies made on a larger scale, some of these deductions seem to be erroneous and misleading.

COMPONENT FACTORS OF CALORIC REQUIREMENTS

In calculating the total caloric requirement of a child there must be taken into account (1) the basal requirement, (2) growth needs, (3) needs for muscular activity, and (4) the food values lost in the excreta. The first of these, the basal requirement, is fairly uniform for children of the same weight. Growth requirements diminish rapidly from birth to the end of the third year and vary but little from this time until the tenth or eleventh year, after which they undergo a marked increase, which is maintained until growth is practically complete. The variation of this growth rate is fairly uniform with all children. Muscular activity, however, varies enormously with different children, but in general tends to increase steadily from birth to puberty. The caloric value of the foodstuff lost in the excreta is subject to very little variation in healthy children of the same age, unless there are marked differences in the diets.

Basal Requirements.—A great deal of accurate information has been accumulated regarding basal requirements, that is, the needs of the body at complete rest. This knowledge has been obtained by calorimetric observations made by Benedict and Talbot, DuBois, Murlin and others in this country and by Voit and Pettenkoffer, Rubner and Heubner, Schlossman and Murschhauser, and Magnus-Levy and others abroad. Some have based their comparison of individuals on the

body surface, but the body weight has been most frequently employed. Many studies have been made of the basal metabolism of adults, both in health and disease, and a large number of observations have been made on infants, especially the new-born. The intervening period, from the age of one year until the end of puberty, has not been so generally investigated. Talbot and Benedict are the only observers who have studied this entire period systematically.

Benedict [1] has recently presented the results of about 250 observations made by himself and Talbot on children of both sexes, more than half of whom were over one year of age. The range of individual
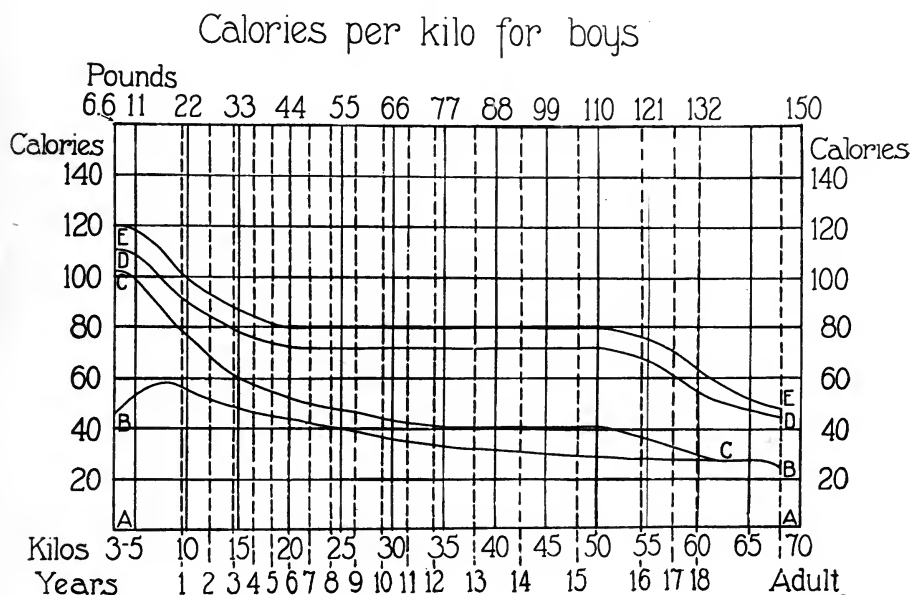
Fig. 1.—The solid vertical lines indicate weights in kilos; the broken lines, approximate weights at each year of age. The space between lines AA and BB shows allowance for basal metabolism; between BB and CC, that for growth; between CC and DD, that for muscular activity; between DD and EE, food values lost in excreta. The space between the lines AA and EE shows the total caloric allowance per kilo.

variation in the values obtained was considerable, but the number of observations made is so large that the data seems sufficient to warrant us in accepting their curves as representing the average for the period of growth.[2] They have shown that the basal metabolism per

_____

1. Benedict, F. G.: Boston M. & S. J. **181**:107 (July 31) 1919.

2. In a personal communication Talbot stated that the curve for the latter years of childhood may need some revision, since up to the present time the number of observations has not been sufficient to establish definitely this part of the curve.

kilo of body weight is at birth "specifically low," that it rises rapidly until the body weight has reached seven to nine kilos and then diminishes slowly to adult life (Charts 1 and 2). There is some difference between the basal needs of boys and girls. After a weight of ten kilos (about one year) is reached the basal requirement of boys exceeds that of girls until a weight of about thirty-five kilos is reached (at about 11 years of age), when the basal needs of girls for a time exceed those of boys. Benedict and Talbot found that the basal caloric requirement increases with age but the relationship is best expressed as calories per unit of body weight or of body surface. There was, in their opin-
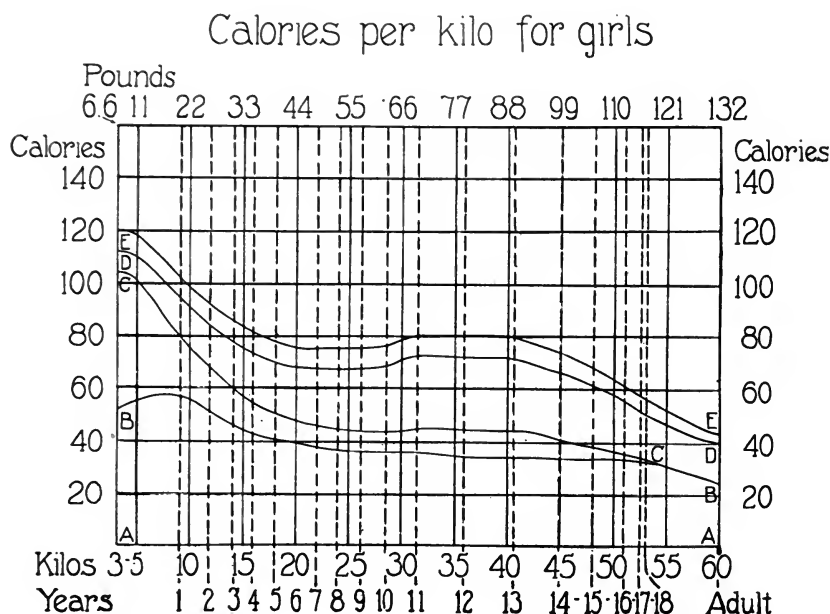
Fig. 2.—The vertical and curved lines have the same significance as in Chart 1.

ion, no closer consistency in the caloric values when expressed per unit of body surface than when expressed per unit of body weight. In our discussion, therefore, we shall use the more convenient standard—the unit of the body weight.

Magnus-Levy [3] in 1899 studied the basal metabolism of twenty-five children of 2 years of age and upward, but the ages studied were widely scattered and the values obtained for different individuals show wide variation. For the most part his values are higher than those obtained by Benedict and Talbot.

3. Magnus-Levy and Falk: Arch. f. Anat. u. Physiol., 1899, p. 314.

DuBois[4] made studies of the basal metabolism of eight boys between 12 and 14 years of age. The values he obtained are also somewhat higher than those of Benedict and Talbot, but are lower than those of Magnus-Levy. Two years later he[5] studied the same boys and found that the basal metabolism per kilo had diminished but that the values obtained fell on the curve which he had deduced, using his own observations and those of others. The reduction in basal calories per kilo in case of these boys was only the normal reduction which takes place steadily with increasing years.

On the whole, it seems reasonable to accept the values for basal requirement given by Benedict and Talbot as representing what they have termed "the irreducible minimum" which must be supplied to the human organism for maintenance.

Growth Requirements.—We shall not at this point consider the special growth needs, such as necessary vitamins or the need of supplying proteins which have the essential amino-acids, but only the energy requirements for growth which are met by the fat, carbohydrate and protein furnished in the ordinary articles of food. The caloric requirements for growth must, it is obvious, be greatest when growth is most rapid and diminish at the period when growth is slower. The rate of growth is most rapid during the first year of life, diminishing greatly in the second year. It is again accelerated at the approach of puberty. The diminution in the growth rate during the early years and the acceleration during the later years is indicated by the annual increase in weight and height from birth up to the time when the body is completely grown. This average increase is shown for both sexes in Chart 3. If we combine the curve representing the annual increase in weight and that for the annual increase in height we obtain a curve which may be taken to represent the annual increase in the size of the body during the period of growth. This rate of increase steadily increases in both sexes after the age of 10. In boys by the sixteenth year and in girls by the thirteenth year it is nearly twice as great as it is at ten years.

In calculating the total caloric requirements in the past it appears that sufficient consideration has not been given to these variations in the rate of growth. The increase in the body's needs for growth is not uniform as age advances from early childhood through the period of adolescence.

Using as a basis for calculation the annual increase in weight, it is possible to estimate very approximately the number of calories needed

4. Dubois, E. F.: Arch. Int. Med. **17**:887 (June) 1916.

5. Olmstead, W. H., Barr, D. P., and DuBois, E. F.: Arch. Int. Med. **21**:5 (Jan.) 1918.
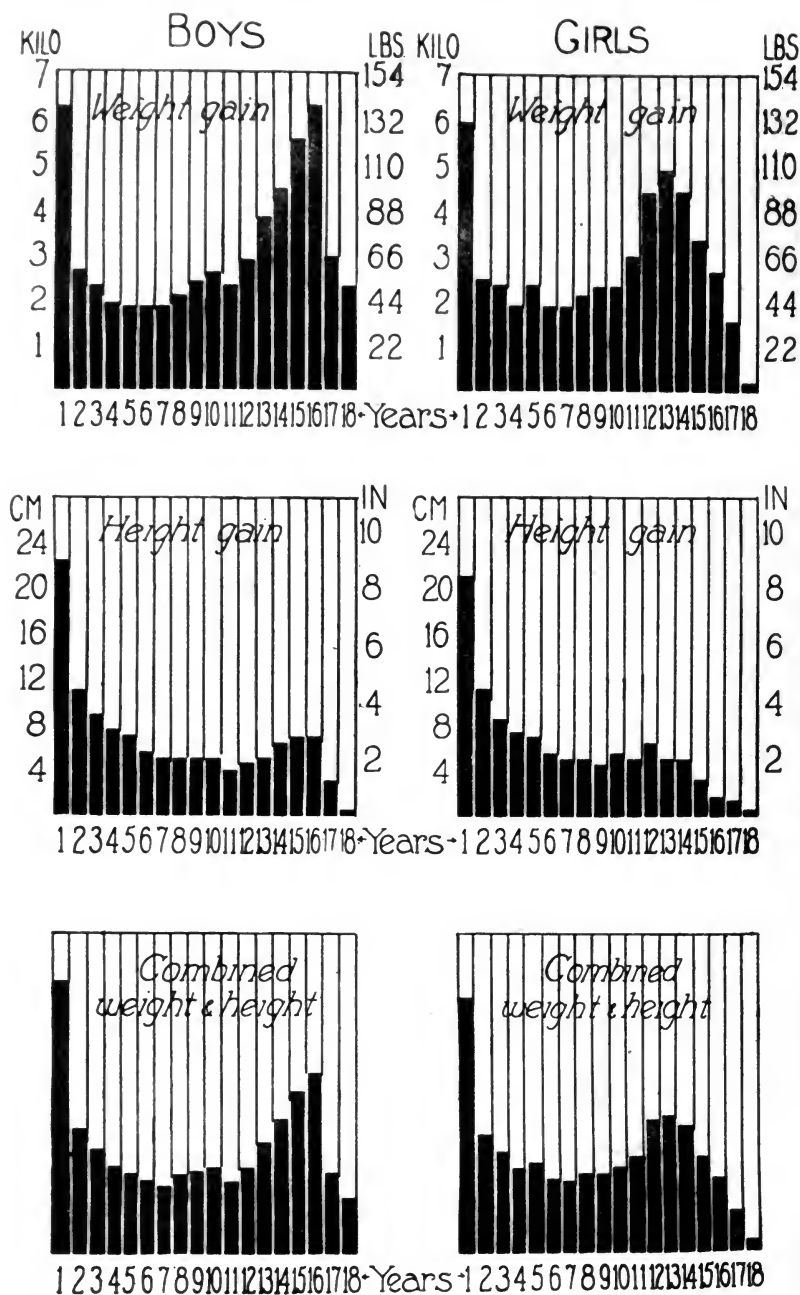
Fig. 3.—The heavy black verticals of the two upper charts show the annual gain in weight in kilos and pounds, and the gain in height in centimeters and inches, for both sexes. The lowest charts show values obtained by combining the two.

for growth by a child at any given age and weight. Rubner [6] estimates that about 80 calories per diem are needed to increase the weight of the human body one kilo in one year. This value multiplied by the average increase in kilos per annum would give approximately the number of calories needed daily for growth. On this basis the daily caloric need for normal growth for boys is over 200 calories during the second year; between 4 and 8 years it diminishes to about 150 calories, then rises steadily, reaching over 500 calories daily during the sixteenth year, after which it rapidly falls (Chart 5).

Requirements for Muscular Activity.—It is difficult to estimate with even approximate accuracy exactly how many calories should be allowed for muscular activity. Allowance must be made for all activity, whether productive or unproductive. Even the energy expended in the process of digestion must be taken into account in estimating these needs. Benedict states that the energy needed to digest the food taken uses up about 6 per cent. of the total calories of the diet. This he terms the "cost of digestion." It is a factor not usually considered but is important. Like the food value lost in the excreta it is one of the inevitable losses and one for which allowance must be made in estimating the total caloric requirement.

The requirements of individual children for activity differ very greatly, more widely than they do in any other respect. A nervous, lively, energetic child will certainly use up more calories in activity than one of quiet, placid temperament and indolent muscular habits. How much the difference is between the actual needs of these two types we can, with our present knowledge, only conjecture.

Lusk [7] has estimated that during the period from four to fifteen years the very active child requires a little more than double the total calories of a quiet child. Since three of the four factors which make up the total calories, namely, basal requirement, growth requirement and the food value lost in the excreta, are nearly the same for these two types of children, it would appear that practically all of the increased allowance which Lusk proposes, or considerably more than half the total food taken, is used up by the very active child in muscular activity. For young children this seems excessive. It certainly cannot be taken as an average. At any age it is probably applicable only to a small group.

Lusk allows for the child of moderate activity about one-third more calories than for the quiet child. This value is probably more nearly correct for the younger children, but the allowance is not enough for boys after 12 years of age and probably not for girls.

---

6. Rubner, M.: Das Problem der Lebensdauer und seiner Beziehung zu Wachstum und Ernährung, 1908.
7. Lusk, G.: J. A. M. A. **70**:821 (March 23) 1918.

A steady increase in the calories which are needed for activity must be allowed as age advances. As soon as a child learns to run about a great increase in activity takes place, and with the normal healthy child activity steadily increases with each year of life, at least up to the period of adolescence.

DuBois estimates that walking at a moderate pace on the level uses three times the basal requirement. On this basis, a boy of about 30 kilos weight, that is, of about 10 years of age, walking on the level for two hours, would require an increase of 270 calories to supply energy for this activity.

The great difference in food requirements of children because of the difference in their activity is not in most cases sufficiently taken into account. If the increased caloric need of the active child is not supplied by the diet, growth inevitably suffers and, as Talbot [8] has pointed out with respect to infants, there is no gain in weight. The same consequence—failure to gain weight——follows when for any reason the digestive organs are not equal to the extra task imposed by increased ingestion of food. All these factors, and not simply the average needs as worked out for large groups, must therefore be taken into account when one is considering the needs of a single child or a small group.

Food Values Lost in the Excreta.—No accurate observations on this point have been published regarding children over 6 years of age. Our own studies lead us to the opinion that this factor varies less with age than do the other three factors which make up the total food requirement, and that in health a loss of calories equal to about 10 per cent. of the food intake is approximately correct for children of all ages. Some variation in children of the same age and weight will of course be seen, depending upon the amount and nature of the food, the care of preparation, on thoroughness of mastication, etc.

Extensive work done by the Department of Agriculture on the diet of adults has established quite definitely that the loss in the excreta, when a mixed diet is taken, averages about 9 per cent. of the total calories ingested. Benedict states that when a mixed diet is properly balanced and the digestion is normal, the loss in the excreta does not average more than 6 per cent. Atwater and Sherman, who followed the metabolism of three six-day bicycle riders, found an average loss in the excreta of nine per cent. of the total calories taken.

Müller [9] made a careful study of the diets of thirty-two children from 2 to 6 years of age. In order to determine the exact food value lost in the excreta, he dried the feces and urine of each child, as well

8. Talbot, F. B.: Am. J. Dis. Child. **18**:4 (July) 1919.
9. Müller, E.: Biochem. Ztschr. **5**:143, 1907.

as a sample of the composite food of each, and determined the exact caloric value of these substances by burning samples in a bomb calorimiter. The average caloric value of the dried feces was 5.0 calories for each gram of dried matter, the range being from 4.6 to 5.4 calories per gram. The urine showed a caloric value ranging from 8.7 to 13.9 calories for every gram of nitrogen which it contained, the average being 10.4 calories per gram of nitrogen. The average daily caloric loss in the feces of the children observed by Müller was 5.9 calories per kilo of body weight. The average loss in the urine was 4.6 calories per kilo of body weight. This gave an average total daily loss in the excreta of 10.5 calories per kilo. The average intake being 103.7 calories per kilo, the average loss in the excreta was, therefore, 10.1 per cent. of the intake. The individual loss ranged from 8 to 14 per cent. of the total caloric intake.

In our own observations we have found that healthy children under 6 years of age taking a mixed diet have from 10 to 20 gm. of dried matter in the daily stools. This represents a loss in the stools of from 50 to 100 calories, using as a basis for calculation Müller's average figure for the caloric value of dried feces. According to our observations, which confirm those of other authors, children from 1 to 6 years of age taking a mixed diet excrete from 4 to 6 gm. of nitrogen in the urine daily. Using Müller's average figure for the caloric value of urine, this indicates a loss of from 40 to 65 calories daily. The combined loss in urine and feces by children from 1 to 6 years of age is, therefore, from 90 to 165 calories daily. This is approximately 10 per cent. of. the calories usually given at these ages, and, therefore, corresponds closely with the value suggested by Talbot for infants.

Using Müller's average caloric values for feces and urine, we have calculated the exact caloric loss through the excreta in five observations on normal children. The loss was found to range in these cases from 8.8 to 10.6 per cent. of the total calories of the food taken and the average was 9.6 per cent. We found that children suffering from a mild form of chronic intestinal indigestion had a loss through the excreta ranging from 10 to 15 per cent. of the total calories taken, while in cases of severe chronic intestinal indigestion the loss was at times as high as 25 per cent. of the total calories of the food taken. A summary of these findings is shown in Table 1.

In cases of severe chronic intestinal indigestion the total food value lost in the stools must frequently be much greater than the 25 per cent. estimated. For in such cases there is usually a very large loss of carbohydrate through fermentation in the intestine. The chief products of this fermentation—gases and volatile fatty acids—do not appear in the dried matter of the stool and we have no convenient method of

estimating them.   Moreover, there is often some loss of protein due to putrefaction, which is represented in the stool mainly by volatile substances.   How many calories these additional losses represent it is difficult to estimate.

TABLE 1.—Average Nutritive Values Lost in Excreta

Condition of Children	Number of Observations	Age in Years	Dried Weight of Feces, Gm. Daily	Calories Lost in Feces	Nitrogen in Urine, Gm. Daily	Calories Lost in Urine	Total Calories Lost in Excreta	Calories in Food Taken	Per Cent. of Calories in Excreta	
									Aver.	Range
Normal.............	5	2-3.5	11.6	58	5.3	55	113	1,177	9.6	8.8-10.5
With mild chronic indigestion.......	10	1-3	14.5	73	4.9	51	124	1,008	12.3	10.0-14.5
With severe chronic indigestion.......	12	2.5-9*	21.1	106	5.8	60	166	865	19.2	12.9-24.7

* Some of the children in this group, although older, were much undersize and underweight and were therefore comparable to those in the other groups.

On the whole, our estimate of 10 per cent. of the calories for loss in the excreta seems a reasonable average allowance for normal children taking a mixed diet.   This allowance would certainly be high for nursing infants, however, since our observations have shown that these infants utilize from 95 to 99 per cent. of the fat intake and a very much higher proportion of the protein intake than do artificially fed infants.

TOTAL CALORIES

A number of authors have made observations on individual children or groups of children to determine the total calories taken at different ages.   A comprehensive survey of the literature on this subject up to 1917 has been made by Lucy H. Gillett.[10]   In her report is given an extensive bibliography and a summary of such values reported by various authors as have been based on actual observations of food taken. Such observations are surprisingly few.   Most of them have been made by the German authors and have been so widely quoted and have formed the basis of so many calculations for total calories per kilo that it seems worth while to go into detail regarding the children studied.   There are objections to using the results obtained with almost all the small groups observed for the determination of the requirements of average healthy children living under normal conditions.

Hasse [11] calculated the calories taken by six girls belonging to well-to-do families.   The ages of these children ranged from 2 to 11 years.   All were in good health, but, as compared with our standards

10. Gillett, L. H.: Publication 115, N. Y. Assn. for Imp. of the Cond. Poor, 1917.

11. Hasse, S.: Ztschr. f. Biol. **18**:553, 1882.

two were under weight, while the others were somewhat over weight. The two under-weight children, who were 2 and 5 years of age, took respectively 102 and 90 calories per kilo, rather high values for their ages. The children of 3 and 3½ years took 77 and 81 calories per kilo, about the usual for their ages. The two older girls, 9 and 11 years of age, took only 65 and 61 calories per kilo, respectively, but these girls were considerably over average weight.

Herbst [12] also observed six children in well-to-do families. Three were boys, aged 2, 4 and 10 years. The youngest was considerably over weight, the other two practically the average weight for their ages. They took respectively 90, 87 and 66 calories per kilo. The other three children were girls in their eleventh, thirteenth and fifteenth years. The first two were very much over weight, the third somewhat over weight. They took respectively 45, 41 and 38 calories per kilo. These values are very low indeed, but the children observed were in a rather exceptional physical condition and data derived from the study of their food can hardly be used as a basis for estimating the needs of the average child. These observations, however, confirm the generally accepted opinion that the food requirements per kilo of over-weight children are much lower than those of children of average weight for their age.

Müller [9] studied twenty-three boys and nine girls, each for a six-day period, and collected and analyzed the urine and feces of each child, as well as recording the exact amount and kind of food taken. The ages of the children ranged from 2 to 6 years. The children were reported to be healthy and free from nutritional disturbances, but all were inmates of an orphan asylum and appear to have been fair examples of what is commonly spoken of as "institution children." Nearly all of the children were under weight, the boys almost without exception markedly so. As might have been expected with children of this class, the intake per kilo was high, the average for the group being 104 calories per kilo. Two-thirds of the boys weighed between 11 and 15 kilos and these boys, all under weight, took on the average 113 calories per kilo. One boy of 4 years with the weight (12.6 kilos) of an average child of about 2 years, took 132 calories per kilo; another child, 6 years old, of about the same weight as the one just mentioned, took 126 calories per kilo.

The girls, who were not so much under weight as the boys, took on the average about 15 calories per kilo less than did the boys. These values correspond fairly well with the usually accepted ones for their ages, except in the single instance of one girl who was about the average weight for her age and who took only 71 calories per kilo.

---

12. Herbst, O.: Jahrb. f. Kinderh. **46**:322, 1898.

Müller's observations were made in winter. He thinks that season should be taken into account in estimating the food needs. His results show that children who are much below normal weight require much more food per kilo than do normal children. All the facts concerning the children observed must be known in order to appreciate and properly interpret the data obtained. We are no more justified in basing our estimates for normal requirements upon the results obtained with these underweight children than on the results with Herbst's overweight girls.

Uffelmann [13] made observations on his own children, all boys, at the age of 2, 4, 10 and 15 years. The oldest and youngest were somewhat, the other two very much under weight. Contrary to general experience, the calories per kilo reported to be taken by these children were low. We can hardly resist the inference that, if the diet at the time of observation was typical of that usually taken, these children were below weight because underfed.

Camerer [14] made extensive observations of the amount of food taken by his own children, four girls and one boy, at different times extending over a period of years. In the observations made at ages under 7 years the calories per kilo taken by both sexes were about the usual for those ages. In the later observations, however, the calories per kilo were very low and diminished rapidly with increasing age, so that in the observations made at ages over 15 years the calories per kilo taken by both sexes were only a little above the basal requirements as determined by Benedict and Talbot. Camerer's girls were on the average much below the average weight for age at the time of observation and during the early years the boy was somewhat under weight. Accordingly a high caloric intake would have been expected. The fact that, on the contrary, the calories per kilo taken by these children were very low suggests, as we have said in regard to Uffelmann's children, that the under weight was possibly due to under feeding.

Baginsky [15] has given values obtained from a study of a number of children convalescent from various forms of acute disease and with one exception much under weight. As might be anticipated, his values are for the most part high.

E. H. Starling,[16] quotes Carl Tigerstedt, who made forty-seven observations on children ranging from 4 to 14 years of age. The weights unfortunately are not given, only the calories per kilo. The striking thing in these observations is the wide range of calories taken.

13. Uffelmann, J.: Hygiene des Kindes, 1881.
14. Camerer: Stoffwechsel des Kindes, 1896.
15. Baginsky, A.: Arch. f. Kinderh. **23**:119, 1897, and **16**:398, 1893.
16. Starling, E. H.: The Feeding of Nations, 1919.

For example, in four observations on children in their fifth year the range was from 73 to 114 kilos; in five observations for the seventh year, from 71 to 102; nine observations for the twelfth year, from 44 to 89; seven observations for the fourteenth year, from 43 to 82 calories per kilo. Starling calls attention to the dangers involved in basing estimates for food requirements on averages, especially when these include only a small number of observations.

In marked contrast to the values found by most of the authors mentioned above are those of Gephart,[17] whose observations were made in quite a different manner. His method was that employed by other writers in studying the actual amount of food consumed by soldiers in camps, and seems to be a reliable way of determining the average number of calories taken. Gephart studied the diet of about 350 boys in a large boarding school (St. Paul's, Concord, N. H). in the following manner: He first calculated the caloric value of the entire amount of food purchased during the period of observation, the entire school year. From this he subtracted the values obtained by analyzing at various times the garbage and the waste. The remainder he divided by the total number of meals served, and thus obtained an average caloric value per meal for the school. In addition to the meals which were provided by the school, the boys were accustomed to buy from a confectioner's shop considerable extra nourishment—sweets, chocolate, cakes, etc. The total amount purchased during the period was known and was apportioned by Gephart among the boys of the whole school. The calories furnished by this additional food were found to be about one-eighth of the total daily consumption.

TABLE 2.—Summary of Gephart's Observations on Boys at St. Paul's School

School	Average Age in Years	Average Weight		Average Calories per Kilo			Average Total Daily Calories
		Kilos	Pounds	School	Food Shop	Total	
Lower...............	13.5	43.6	96	98	15	113	4,949
Middle..............	14.5	50.8	112	88	13	101	5,126
Upper...............	16.1	60.6	133	71	11	82	4,997

. The average daily caloric intake was found to be about 5,000 calories per boy, and all but the group of the oldest boys took over 100 calories per kilo. The boys were divided into three groups, the lower, the middle and the upper school. In Table 2 are given the ages, average net weight, calories per kilo furnished by the school, additional calories purchased at the confectioner's, average total calories per kilo and average daily total calories for each group.

17. Gephart, F. C.: Boston M. & S. J. **176**:17, 1917.

While the conclusions which might be drawn from these observations may perhaps be open to question, still, the results show what amount of food is actually taken by the average American school boy at the ages studied, under the special conditions represented by these observations. It may be argued that these conditions were not average but somewhat exceptional. The boys were living in a rigorous climate; they were taking a great deal of active out-of-door exercise and they were at an age when growth is most rapid. Furthermore, the well-known disposition of boys of these ages to stuff themselves with food apparently beyond their actual needs must also be taken into account. Still when due allowance has been made for all these conditions, the fact remains that the enormous appetite of active, growing boys represents a physiological need which in the past has not been given sufficient consideration.

Studies made on such large groups are likely to give results much nearer the truth than observations made on a few individuals or the children of one family, no matter how carefully these observations have been made. The results of the German observations which we have quoted would lead one to allow too little food for children during the active growing period.

The Department of Agriculture has made many observations on the amount of food taken by families, including children, but has not determined experimentally what proportion of the food was taken by each child. They have apportioned the diets theoretically according to a commonly used system of coefficients; for example, assuming that if a man takes one portion, a woman takes 0.8, a boy of 12 takes 0.8, a boy of 8 takes 0.7, etc.

Schedules Proposed by Various Authors.—Several authors have proposed complete schedules of theoretic caloric requirements from infancy to adult life. These have been based either on their own observations or on those of others. Most of these observations we have just discussed.

Among the German observers, Camerer's schedule has been most often quoted as a standard. His suggested allowance for boys is 89 calories per kilo at the age of one year and diminishes to 75 calories at 4 years. For the age of 5 years the allowance is increased to 84 calories. From that age the allowance decreases rapidly and steadily to adult life. His values after 6 years are low, and after 9 years extremely so. After the twelfth year his allowance is but little above the basal requirements as shown by Benedict and Talbot.

Steffen [18] offers a schedule for children up to six years of age and allows over 100 calories per kilo through this entire period.

---

18. Steffen, W.: Jahrb. f. Kinderh. **46**:332, 1898.

Uffelmann has proposed a schedule for the first five years of life. His values are rather low, ranging from 88 calories per kilo at one year to 68 calories at five years.

Gillett and Sherman, after giving due consideration to the observations which have been published and which are summarized by Gillett, present a table of suggested values for total daily calories for children of both sexes throughout the entire period of growth. They allow a considerable range of variation. Their allowance diminishes gradually to 68 calories per kilo at 9 years and is maintained at that figure up to the age of 13, dropping to 65 at 14 years. After this age the average allowance is rapidly decreased to 55 calories per kilo at 16 years. This decrease in calories per kilo during the period of most rapid growth after the age of 13 seems to us injudicious.

Lusk has recently published estimates for total calories. As already mentioned, he makes a very large allowance for activity and gives three curves—for the quiet child, the active child and the very active child. He allows the same percentage increase in total calories for increased activity, quite irrespective of age and weight. That is, his values for the active child are about one and one-third times those for the quiet child at all ages, while the values for the very active child are about twice those for the quiet child at all ages. Accordingly, his estimates for total calories for the very active child and even for the child of moderate activity, are extraordinarily high for the early years, for example, 193 and 129 calories per kilo, respectively, for a boy of 2 years. The diminution in calories per kilo with increasing years is rapid according to all three of his curves. His values for the quiet child after the age of 13 are very little above the calories necessary for basal metabolism and for normal growth. No allowance is left for activity, which of course can never be reduced to zero.

Gillett and Sherman and also Camerer give schedules for girls as well as for boys. According to both the allowance for girls is considerably lower than that for boys, and from the twelfth year the allowance exceeds only by very little the needs for basal metabolism and growth.

PROPOSED SCHEDULES FOR CALORIES PER KILO

In the light of our own observations and those of others, the theoretical schedules for calories per kilo of body weight shown in Charts 1 and 2 and Tables 3 and 4 are suggested. The charts show the curves and the tables the actual figures, on which the curves are based, for the different factors which make up the total calories per kilo. The tables show also the percentage allowance for each of the different factors.

TABLE 3.—Suggested Calories per Kilo for Boys

Weight, Kilos	Calories per Kilo					Per Cent. of Calories for				Total Calories Daily
	Basal	Growth	Activity	Excreta	Total	Basal	Growth	Activity	Excreta	
3	46	56	8	10	120	38	47	7	8	360
4	50	52	8	10	120	42	43	7	8	480
5	54	46	8	10	118	46	39	7	8	590
6	56	38	10	10	114	49	33	9	9	685
7	57	32	11	10	110	52	29	10	9	770
8	56	28	12	10	106	53	26	11	10	850
9	55	25	12	10	102	54	24	12	10	920
10	54	22	13	10	99	55	22	13	10	990
11	53	19	14	10	96	55	20	15	10	1,000
12	52	16	16	9	93	56	17	17	10	1,120
13	51	14	17	9	91	56	16	18	10	1,180
14	50	13	17	9	89	56	15	19	10	1,240
15	49	12	17	9	87	56	14	20	10	1,300
16	48	10	18	9	85	56	12	22	10	1,360
17	47	9	19	8	83	56	11	23	10	1,410
18	46	8	20	8	82	56	10	24	10	1,470
19	45	7	21	8	81	56	9	25	10	1,540
20	44	7	21	8	80	55	9	26	10	1,600
22	42	7	23	8	80	53	9	28	10	1,760
24	41	8	23	8	80	51	10	29	10	1,920
26	39	8	25	8	80	49	8	31	10	2,080
28	38	7	27	8	80	47	9	34	10	2,240
30	36	7	29	8	80	45	9	36	10	2,400
33	35	7	30	8	80	44	9	37	10	2,640
36	33	8	31	8	80	41	10	39	10	2,880
39	32	9	31	8	80	40	11	39	10	3,120
42	31	10	31	8	80	39	12	39	10	3,360
45	30	11	31	8	80	38	13	39	10	3,600
48	30	11	31	8	80	38	13	39	10	3,840
51	29	11	31	8	79	38	13	39	10	4,030
54	29	8	31	8	76	38	11	41	10	4,100
57	28	5	30	7	70	40	7	43	11	3,990
60	27	2	27	7	62	43	3	44	10	3,720
68 (Adult)	25	0	18	5	48	52	0	38	10	3,265

TABLE 4.—Suggested Calories per Kilo for Girls

Weight, Kilos	Calories per Kilo					Per Cent. of Calories for				Total Calories Daily
	Basal	Growth	Activity	Excreta	Total	Basal	Growth	Activity	Excreta	
3	51	51	8	10	120	43	43	6	8	360
4	53	49	8	10	120	45	41	6	8	480
5	55	45	8	10	118	47	38	7	8	590
6	56	38	10	10	114	49	33	9	9	685
7	56	33	11	10	110	51	30	10	9	770
8	57	27	12	10	106	54	25	11	10	850
9	56	24	12	10	102	55	23	12	10	920
10	55	21	13	10	99	56	21	13	10	990
11	53	19	14	10	96	55	20	15	10	1,060
12	51	17	16	9	93	55	18	17	10	1,120
13	49	16	16	9	90	54	18	18	10	1,170
14	47	14	17	9	87	54	16	20	10	1,220
15	45	12	19	8	84	54	14	22	10	1,260
16	44	11	19	8	82	54	13	23	10	1,310
17	43	10	19	8	80	54	12	24	10	1,360
18	42	9	19	8	78	54	12	24	10	1,400
19	41	8	20	8	77	53	11	26	10	1,460
20	40	7	21	8	76	53	9	28	10	1,520
22	38	8	22	8	76	50	11	29	10	1,670
24	37	8	23	8	76	49	11	30	10	1,820
26	36	8	24	8	76	48	10	32	10	1,980
28	36	8	25	8	77	47	10	33	10	2,155
30	36	9	26	8	79	46	11	33	10	2,370
33	35	10	27	8	80	44	12	34	10	2,640
36	35	10	27	8	80	44	12	34	10	2,880
39	35	10	27	8	80	44	12	34	10	3,120
42	34	9	27	8	78	44	11	35	10	3,275
45	34	7	26	7	74	46	9	35	10	3,390
48	33	5	22	7	67	49	8	33	10	3,215
51	32	3	21	6	62	51	5	34	10	3,160
54	31	0	18	5	54	57	0	33	10	2,915
60 (Adult)	25	0	15	4	44	57	0	33	10	2,640

The basal requirement adopted is that of Benedict and Talbot. This, it will be seen, after reaching a maximum at about the ninth month, falls steadily through the entire period of growth to adult life. The basal requirement per kilo for girls is lower than that for boys up to the age of 11 years, after which it is higher than that for boys until the completion of growth.

The growth allowance has been calculated from the average normal rate of growth, which has been well established. The calories allowed for growth fall steadily from the first year to the sixth year, then remain practically constant up to eleven years for girls and thirteen years for boys, when a marked increase takes place. This increased need is evident for about three years with both sexes, after which the growth needs rapidly diminish to zero.

The needs for basal metabolism and for growth, though subject to considerable individual variation, are, as averages, practically irreducible.

The allowance for activity is admitted to be hypothetical. For reasons previously given, this has been increased steadily from the second to the thirteenth year for boys and to the twelfth year for girls. Whether the allowance for activity should be further increased during the period of most rapid growth (in girls from the twelfth to the fourteenth or fifteenth year and in boys from the thirteenth to the seventeenth) is somewhat doubtful. It is a matter of common observation that while the body is increasing so rapidly in size as it does at this time, "the lazy age," there is frequently seen in both sexes a growing disinclination to active muscular exertion, which is usually accompanied by a corresponding disinclination to mental activity, sometimes amounting almost to mental lethargy. A very considerable stimulus may be needed to voluntary effort, both mental and physical. This is not surprising; it is rather to be expected and may be considered physiologic. The opinion is not only an impression from our own observations but is confirmed by the head masters and athletic directors of six large schools for boys with whom we have discussed the question. For the reasons above given we have felt that no increase in the caloric allowance per kilo for activity should be made during these years of most active growth; possibly even a slight reduction should be considered.

The number of calories we have allowed for loss in the excreta is 10 per cent. of the total after the first year of life, during which period a somewhat smaller proportion should be allowed, certainly for nursing infants.

With the values proposed for the different factors just discussed the total calories per kilo are for both sexes about 120 during the

early part of the first year, diminishing to 100 at one year, and reaching 93 calories per kilo at 2 years. After the second year there is an appreciable difference between the total calories per kilo allowed for boys and for girls, owing largely to the difference in their basal requirement, that of girls being, from this time until the end of the tenth year, several calories lower than that of boys. The calories per kilo allowed for both sexes slowly fall, largely because of the slowing up of the growth rate. We have estimated that at 6 years the total for boys should be 80 calories per kilo and for girls 76 calories per kilo. This value we have continued for boys up to about the sixteenth year. For girls the calories per kilo have been increased from 76 to 80 during the eleventh year, since there is at this time an increased growth need and since the basal needs for this and the next few years are nearly uniform. This higher value is continued for girls to about the fourteenth year. After the sixteenth year in boys and the four·· teenth year in girls, since there is a rapid decline in growth needs and possibly some reduction in activity, the total calories per kilo have been rapidly reduced to adult standard—about 48 for males and 44 for females.

The chief difference between our schedule for total calories per kilo and others which have been proposed, is that in our schedule the total calories per kilo are nearly uniform from the age of six to the end of the period of rapid growth.

In the practical application of these suggested values it must be borne in mind that each component part of the caloric requirement is subject to considerable individual variation. The curve suggested aims only to give averages. The calories actually given must vary to fit the individual needs. Activity is of course the most obvious variant. An extremely active child will undoubtedly utilize more calories than the average which we have allowed, while the needs of a quiet child may be supplied by somewhat less than our suggested values.

Another cause for variation in the caloric requirement for the individual is the relation of weight to height and age. Our observations and those of others show that the underweight child will take and utilize more calories per kilo than the child of average weight; while, as might be expected, one who is overweight does not take and does not need the average number of calories per kilo. The fact must be taken into account in making the caloric allowance for an individual child.

It seems reasonable to allow for the younger children a normal range of five calories per kilo above and below the average given, and to allow the older children a range of eight to ten calories above and below the average. For instance, the normal range allowed for a

boy of 2 years might be from 88 to 98 calories per kilo, for a boy of six from 72 to 88 calories and for one of 15 a range from 70 to 90 calories per kilo. When activity is excessive, however, an increase of 20 or even 30 calories above the average may be well utilized.

Comparison of Schedules Proposed.—In order to show the difference between our suggested schedule for calories per kilo and others which have been proposed, Table 5 and Chart 4 are given. The table shows the calories per kilo proposed by various authors for both boys and girls at different ages. This table brings out clearly the points already mentioned in discussing the schedules offered. The only schedule which allows more calories per kilo throughout the entire range of years than does ours is that of Lusk for the very active child. During the early years this schedule shows about twice as many calories per kilo as we have considered sufficient. The difference diminishes after the age of seven, until at the age of fifteen his values are but little above ours. Lusk's estimate for the child of moderate activity exceeds ours up to the age of twelve, after which his values fall considerably below ours. The other complete schedules, those of Gillett and Camerer, are much below ours after the age of seven or eight. The two schedules for girls show values very much below ours after the age of six years.

TABLE 5.—COMPARISON OF SCHEDULES FOR TOTAL CALORIES PER KILO

Author	Age, Years															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Boys:																
Holt and Fales.........	100	93	88	84	82	80	80	80	80	80	80	80	80	80	80	75
Gillett...................	105	90	83	79	77	75	73	71	68	67	68	69	68	65	60	55
Lusk, quiet child........	79	97	90	88	79	78	79	73	70	66	66	62	54	48	45	
Lusk, active child.......	...	129	117	116	105	105	105	97	93	88	83	82	73	66	62	
Lusk, very active child..	...	193	177	175	158	158	159	146	139	132	124	123	109	98	93	
Camerer..................	89	80	78	75	84	77	72	67	63	58	55	52	49	47	45	42
Uffelmann...............	88	80	73	71	68											
Steffen..................	113	99	105	125	114	103										
Girls:																
Holt and Fales.........	101	94	87	82	78	76	76	76	76	77	80	80	79	74	67	62
Gillett..................	105	93	83	79	73	71	69	66	64	62	59	55	51	49	47	46
Camerer.................	89	80	78	75	70	67	64	62	60	58	55	51	47	43	41	39

On Chart 4 the basal metabolism and the growth needs are indicated by the heavily and lightly shaded areas respectively. As we have said, these are, as averages, practically irreducible. The various curves shown in the chart were obtained by plotting the values offered in the various schedules after subtracting the ten per cent. of the total calories which is lost in the excreta. Therefore, the space between the shaded areas and the various lines represents the allowance for activity according to the different authors. The great difference is at once apparent. The curves representing total calories per

kilo would be obtained by raising each of the curves shown by the addition to the values plotted of the ten per cent. allowance for loss in the excreta.

The curve based on Camerer's values shows very little allowance for activity except between the ages of 4 and 8 years and after the age of 13 years practically none at all.

The curve based on the average values offered by Gillett and Sherman does not differ greatly from our own up to the age of 7 years. From 7 to 14 years it is nearly parallel with ours, but somewhat
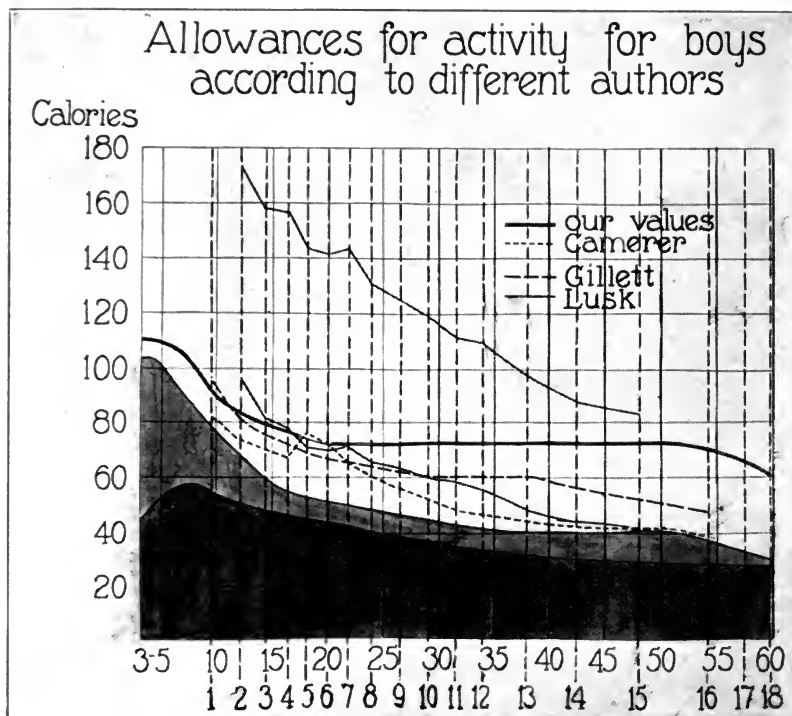
Fig. 4.—The heavily shaded area represents allowance in calories per kilo for basal metabolism; the lighter shaded area, the allowance for growth; both areas are according to our schedule. The spaces between the shaded areas and the lines above show what remains for activity according to the estimates of different authors. The solid vertical lines indicate weight; the broken lines, approximate weight at each year of age.

lower. After 14 years their curve falls rapidly. In our judgment they have allowed far too little for activity and growth during adolescence. As previously stated, they allow a fairly wide individual variation in total calories, but even if their maximum allowance is taken, the calories per kilo after the age of 14 are only about five

calories higher than the values shown on the chart, and therefore, still about fifteen calories per kilo lower than the values we have suggested.

The curve based on Lusk's values for the quiet child is almost identical with our own from 2 to 7 years. After this age his allowance for activity diminishes very rapidly and becomes practically zero at fourteen years. He gives a schedule, not represented here, for the child of moderate activity which, when plotted, is represented by a curve almost parallel to the one just discussed but about one-third higher. His curve for the very active child seems to give an extreme allowance for activity, certainly for the first ten or twelve years of life. At the age of 15 his allowance is not far above our own.

Total Daily Calories.—Charts 5 and 6 and Table 6 gives for boys and girls the average values for total daily calories based upon the values for calories per kilo just proposed by us. The curves shown on the chart are plotted on the basis of years of age, using the average normal weights at the different ages. The charts show not only the total daily calories but also the components—basal needs, growth needs, allowance for activity and for loss in the excreta—which together make up the total.

TABLE 6.—SUGGESTED TOTAL DAILY CALORIES

Age Years	Boys					Girls				
	Average Weight		Calories per		Total Daily Calories	Average Weight		Calories per		Total Daily Calories
	Kilos	Pounds	Kilo	Pound		Kilos	Pounds	Kilo	Pound	
1	9.5	22	100	45	950	9.3	21	101	45	910
2	12.2	27	93	42	1,135	11.8	26	94	43	1,110
3	14.5	32	88	40	1,275	14.1	31	87	40	1,230
4	16.4	36	84	38	1,380	15.9	35	82	37	1,300
5	18.2	40	82	37	1,490	18.2	40	78	36	1,410
6	20.0	44	80	36	1,600	20.0	44	76	34	1,520
7	21.8	48	80	36	1,745	21.8	48	76	34	1,660
8	24.0	53	80	36	1,920	23.9	53	76	34	1,815
9	26.4	58	80	36	2,110	26.2	58	76	34	1,990
10	29.1	64	80	36	2,330	28.5	63	77	35	2,195
11	31.4	69	80	36	2,510	31.5	69	80	36	2,520
12	34.2	75	80	36	2,735	35.8	79	80	36	2,864
13	38.0	84	80	36	3,040	40.6	89	79	36	3,210
14	42.5	94	80	36	3,400	45.0	99	74	34	3,330
15	48.2	106	80	36	3,855	48.3	106	67	30	3,235
16	54.5	120	75	34	4,090	51.0	112	62	28	3,160
17	57.5	127	69	31	3,945	52.6	116	58	26	3,060
18	59.8	132	62	28	3,730	52.8	117	56	25	2,950
Adult	68.0	150	48	22	3,265	60.0	132	44	20	2,640

The daily calories allowed for the boys and girls are about 950 at one year. They increase with succeeding years for both sexes, the increase for the boys being a little more rapid than for the girls until the age of 12 is reached. From 12 to 14 the total calories for the girls exceed those for boys. After fourteen, the allowance for boys is considerably greater than that for girls. The highest values for daily
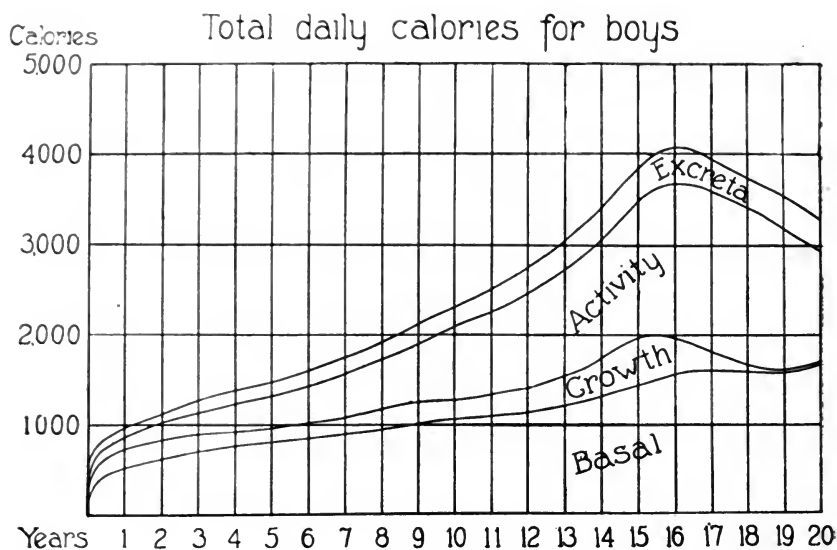
Fig. 5.—The distance between the base and the upper line shows the allowance for total daily calories according to age, from birth to adult life. The spaces between the various lines, from the base line upward, indicate the allowance for the different factors which make up the total, namely, for basal requirement, growth, activity and loss in excreta.
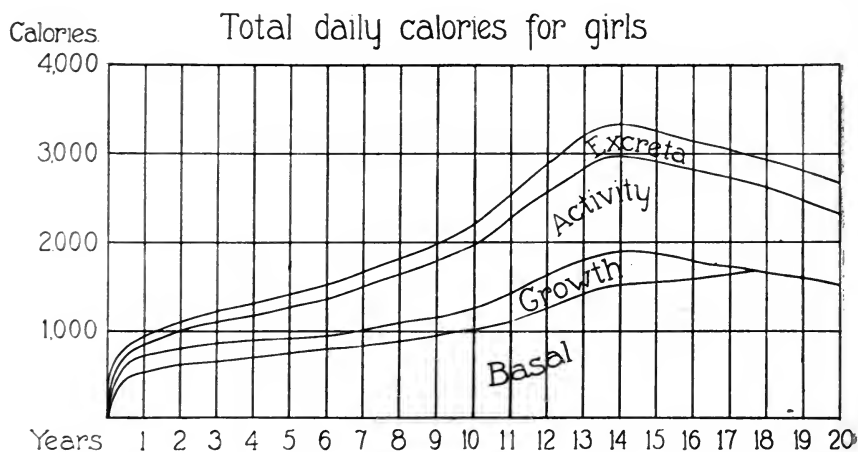
Fig 6.—The curved lines and spaces have the same significance as in Chart 5.

calories are 3,330 for girls at the age of 14 and 4,100 for boys, at the age of 16. After these maximum figures are reached the values drop very rapidly to adult standards for moderate activity,—about 2,640 for women and 3,265 for men.

These charts show the provision for the increase in the growth needs during the period of adolescence. The growth need, calculated according to Rubner's formula, reaches for girls 380 calories daily during the thirteenth year, and for boys about 500 calories daily during the sixteenth year. It is this greatly increased need of calories for normal growth at this period that has not been sufficiently taken into account by many authors in estimating the total daily calories required by the growing child.

The large allowance for activity is of course the most debatable factor in our estimate. Some may think that this allowance is excessive but the more recent observations, particularly those of Gephart, seem to justify our position. Our values for the total daily caloric allowance for boys of the age of those studied by Gephart are still much below the calories which he found to be actually taken by the boys he observed. However, as we have stated, these boys were living under rather exceptional conditions and the calories taken by them can hardly be used as a basis for estimating normal averages.

According to our schedule the allowance for activity varies from 6 per cent. of the total calories during the first year to a maximum of 44 per cent. of the total calories during the period of adolescence. This does not seem excessive for this active period.

It is a common observation and an undoubtedly true one, that during adolescence the average boy or girl takes more food than the average adult man or woman. Unquestionably, this represents a real physiologic need. It is only by assuming such values for calories per kilo as we have proposed that one can reach a total daily caloric intake which will be in accord with these conditions.

The several authors who have given complete schedules for food requirements steadily increase the total daily calories with age through childhood and adolescence up to the standard allowance for adults. No one has up to the present proposed a schedule according to which the values for total daily calories exceed adult standards during adolescence and drop to adult standards with the completion of growth. This seems to us to be absolutely necessary. Unless this is done, the increasing growth needs must be deducted from the allowance for activity, leaving for the latter a very small remainder; or, on the other hand, if activity is maintained, growth must suffer. The modern child, boy or girl, is usually an active person during adolescence. If in school, he is required by school routine to take systematic exercise. If he has left school and entered industrial life he may be con-

tinually compelled to expend physical energy. In view of these facts it is evident that the food taken by perhaps the majority of boys of the poorer classes who are engaged in active industrial occupations during this period of rapid growth, is totally inadequate. An arrest of growth is the almost inevitable consequence of forced activity on a limited ration.

<div align="center">ORIGINAL OBSERVATIONS</div>

Because there have been so few observations reported in the literature which give the calories taken by normal children under average conditions and because of the objections, already discussed, to drawing conclusions from a small number of observations, we have endeavored to collect a sufficient number of individual diet records to warrant some conclusions. This has proven to be a laborious and difficult task. We have at present, however, obtained dietary records from over one hundred selected children of both sexes from 1 to 16 years of age, who were healthy, well cared for, and normal as to digestion. They were almost all children in private families, living in excellent surroundings. The parents were intelligent people, interested in the purpose of our experiment, and willing to cooperate. The children were supposedly intelligently fed and it can be assumed that they were receiving diets fairly typical of those usually taken by well children.

A report of the net weight, height, activity, appetite, general condition, etc., was obtained, together with a record of the exact amount of each item of food taken by the child for four consecutive days. From these data the caloric value of the average daily diet was calculated. Not only was the value for the total calories obtained, but also the distribution of the calories as fat, carbohydrate and protein, which, together with other facts brought out, will be discussed in succeeding papers. Established caloric values of the common articles of food have been compiled in a convenient form by Locke.[19] These have been for the most part used. Other authors whose publications we have found valuable for reference in this study are Leach,[20] Sherman,[21] Lusk[22] and Jordan.[23] The values of a number of articles were calculated from the results of analyses made in our own laboratory.

This method of estimating the calories taken by children is of course not absolutely accurate but it undoubtedly gives a very close approximation. While there are slight variations from the usual caloric values of the food taken owing to differences in the methods of

19. Locke, E. A.: Food Values, 1917.
20. Leach, A. E.: Food Inspection and Analysis, 1920.
21. Sherman, H. C.: Chemistry of Food and Nutrition, 1919.
22. Lusk, G.: The Science of Nutrition, 1919.
23. Jordan, W. H.: The Principles of Human Nutrition, 1919.

preparing food, it is probable that these errors tend to balance each other and that the net result is approximately accurate. We feel certain that in no case did the child receive less food than was reported. It is not unlikely that in some cases a child actually took more food than was reported, especially the older children whose diet is not so carefully supervised and who are more likely to eat between meals without the knowledge of the parent. If there is, therefore, an appreciable error in the estimation of the calories, it is that the calculated amount is somewhat low.

The largest number of the records were of children under 11 years of age. There are from five to twelve observations for each year up to the age of 11. Beyond this age the number of observations for each year is too small to warrant definite conclusions.

In Chart 7 are shown the total calories taken by these children arranged according to age. The curves shown are those based upon the schedules proposed by us for average daily calories at different ages. The curve for boys is indicated by the solid line, that for girls by the broken line. The individual observations for boys are shown by the dots, those for girls by circles.

This chart shows, as was to be expected, a wide variation in individual observations. However, the observations mostly fall near the curves and up to the age of 11 the average would fall very near the curves. Beyond that age there are as yet too few observations to be conclusive. However, those made on older boys are very close to the proposed curve.

Some of the observations which vary most widely from the average curves deserve special mention. There were eight children in the series whose total calories taken amounted to over one-third more than the theoretical average requirement, but every one of these children was reported to be exceedingly active. There were only two children, both girls, whose total calories were more than one-third less than the theoretical average requirement, but these girls were both very large for their ages, in fact, had nearly attained adult stature and accordingly did not need the number of calories for growth usual for that age.

On the whole, it would seem that the curves suggested are approximately correct for the average caloric requirements up to the age of 11 years. We feel confident that a larger number of observations for the later years will verify the estimates for those years also.

When the individual observations are considered on a per kilo basis and compared with the proposed curves for calories per kilo, the individual observations show wide variation, but practically all the high values for calories per kilo were found in case of very

Total daily calories — 100 individual observations
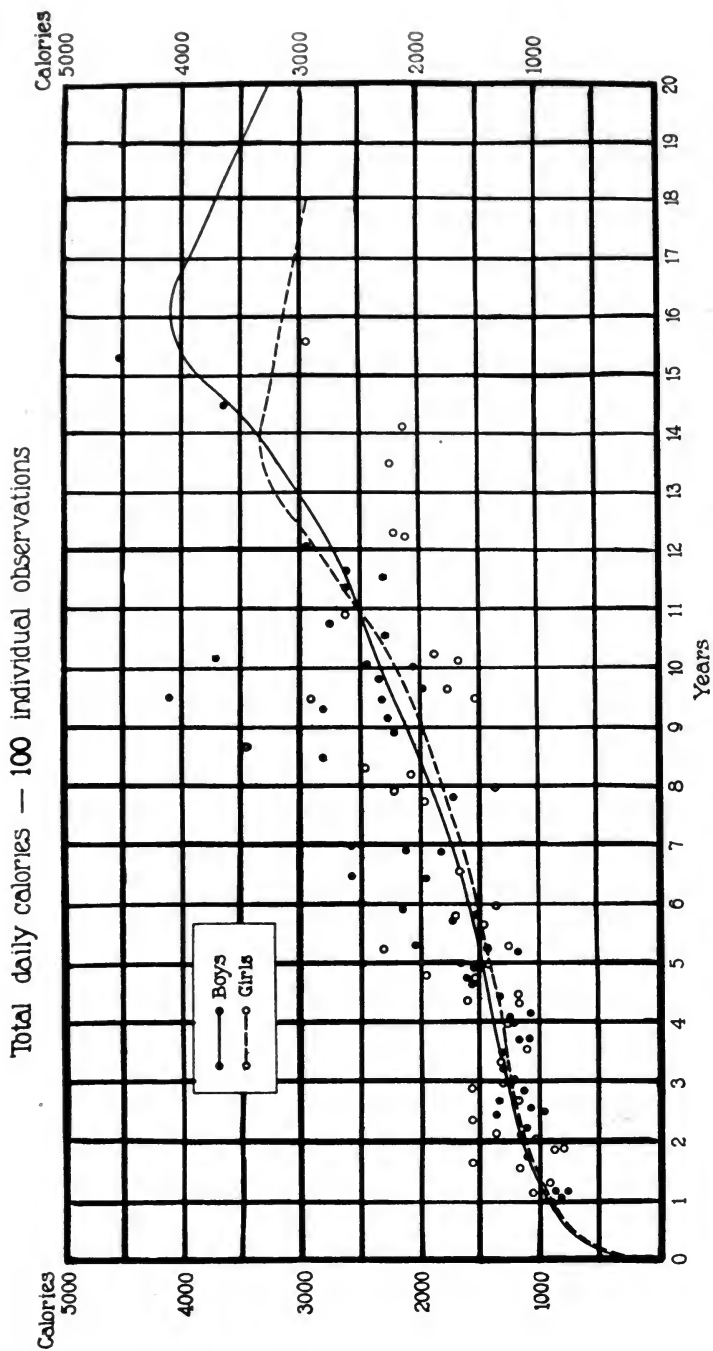
Fig. 7.—Curved lines represent suggested total daily calories according to age, the solid line the curve for boys, the broken line for girls. The dots represent the calories taken in individual observations on boys, the circles those taken by girls.

active children or those who were very much under weight for their height or undersize for their age. The values which were found to be much lower than the average shown by the curves were mostly in case of quiet children or those who were either large for their age or over weight for their height.

SUMMARY

1. In calculating the total caloric requirements of children there must be considered separately the component parts of which the total is made up. These are the requirements for basal metabolism, for growth, for muscular activity and the food values lost in the excreta.

2. The basal requirements, which have been determined by Benedict and Talbot, are highest per kilo at about nine months and steadily fall from this time up to adult life.

3. The food value normally lost in the excreta is a nearly uniform proportion of the intake, about 10 per cent., for all ages after infancy.

4. The requirements for growth are greatest during the period when growth is most active, namely, during the first year of life and during adolescence. They are nearly uniform from the fourth to the tenth or eleventh years.

5. The average for three factors—basal, growth requirements and food values lost in excreta—are nearly uniform for children of the same weight living under similar conditions.

6. The requirement for activity is the only factor which varies widely with different individuals.

7. The great differences in the calculations of different writers who have estimated theoretical values for total calories per kilo for children are in part due to the fact that they have not sufficiently considered the different component parts which make up the total.

8. The average caloric requirement of children according to our observations is about 100 calories per kilo at an age of 1 year (about 9.5 kilos). For boys it falls to about 80 calories at 6 years (about 20 kilos) and remains practically constant at this value up to the age of 15 years, the increasing requirements for activity being met by the reduction in basal requirements per kilo. After a weight of 50 kilos (about 15 years), is reached the calories per kilo can rapidly be reduced to adult standards, about 48 calories per kilo. The requirement for girls falls to 76 calories per kilo at 6 years (about 20 kilos), continues at this value until the tenth year. During the tenth year it rises because the basal requirement is nearly constant while there is an increase in needs for growth and activity. The requirement remains at 80 calories per kilo until growth is complete, then falls rapidly to adult standards, about 44 calories per kilo.

9. In our calculation we have allowed a much higher value for calories per kilo during adolescence than have others. This seems to be absolutely essential, because of the increased growth needs at this time and the large requirement for muscular activity.

10. According to our allowance the total daily caloric requirement of children of both sexes during adolescence exceeds by nearly 1,000 calories the requirements of the adult man or woman of moderate activity.

11. Children who are under weight require more calories per kilo than those who are of average weight for their age. Children who are over weight require fewer calories per kilo than those of average weight.

12. The schedule here proposed is a tentative one and is based on present knowledge, which is in many respects incomplete. There are a number of points which must be studied more fully before definite standards can be established.

For the many reasons which we have discussed, it seems the right procedure to allow for children during the period of adolescence more calories than the adult ration and, as growth needs end, to diminish the caloric allowance to the adult standard. We quite agree with Benedict's recent statement, "It is still, however, the best practice to give a most liberal diet to children, since the greater part of the evidence on under weight indicates that children usually receive too little rather than too much food."

CALCIUM IN THE BLOOD OF CHILDREN *

W. DENIS, Ph.D., and FRITZ B. TALBOT, M.D.

BOSTON

The publication of several relatively accurate and simple micro-methods for the determination of calcium in the blood has opened the way for many interesting lines of investigation in the field of calcium metabolism. About two years ago, inspired by the acquisition of a new weapon, we embarked on the study of an old and much investigated problem, viz., the calcium metabolism of children. The obvious connection between rickets, and probably infantile tetany, and some error of calcium metabolism, has naturally led us to lay special stress on the study of patients suffering from these disorders, but we also have attempted to collect data on the calcium content of the blood of children suffering from a variety of pathological conditions.

Our calcium determinations have been made by the method of Lyman,[1] which we have modified in a few minor details. Lyman's method for the determination of calcium in blood consists essentially in the following steps: the removal of protein by precipitation with trichloracetic acid, the precipitation of calcium from the protein-free filtrate, as calcium oxalate, by means of the technic of McCrudden, the transformation of the calcium so precipitated into colloidal calcium stearate, and the nephelometric determination of the same. The experience gained during several years' use of this method has led us to adopt the following modifications: First, the employment of citrated plasma, (0.1 gm. of solid sodium citrate to 10 c.c. of blood), as preliminary experiments convinced us that no calcium was precipitated by the use of this amount of sodium citrate, and that as pointed out by Halverson[2] and his collaborators, the determination of calcium in plasma or serum is of more significance than when made on whole blood as originally recommended by Lyman. Second, the use of a variety of standards for the final nephelometric reading. Lyman recommends the use of a single standard, equivalent to 0.2 mg. of calcium. While this standard is well suited for work with normal material, in cases where the amount of calcium is much reduced, it is impossible to obtain accurate results by its use. We have, therefore, adopted the plan of invariably preparing three standards for every

1. Lyman, H.: J. Biol. Chem. **29**:169, 1917.

2. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: J. Biol. Chem. **32**:171, 1917.

determination, or series of determinations. These standards are made up to contain 0.20, 0.15, and 0.10 mg., respectively, of calcium. If this assortment of standards is provided it is always possible to obtain readings within 20 per cent. of the unknown, whereas, if only one standard is made, many determinations must be discarded simply because of the wide deviations between the reading of the standard and that of the unknown. The magnesium determinations were made by a method recently described by one of use.[3]

In Table 1 we have collected the results obtained from the examination of 119 samples of blood taken more or less at random from patients in the children's ward of this hospital. These figures are arranged according to the level of plasma calcium without regard to the diagnosis.

Such a series of analyses is of value in that they furnish a fair idea of the variations to be expected in unselected hospital material. An inspection of these results shows a maximum figure of 13.5 and a minimum of 1 mg. of calcium per hundred c.c. of blood plasma, figures which represent an enormous range. Further analysis gives the distribution as shown in Table 2.

It is to be regretted that we were unable to make observations on strictly normal children. It may safely be assumed that many of our cases were normal in so far as there existed any possibility of the presence of an abnormality of calcium metabolism, but as these subjects were inmates of a hospital ward we scarcely feel justified in collecting such cases into a "normal" group.

For comparison we have to rely on a series of figures obtained on twenty-two normal adults in which the maximum figure was 12.1 mg., the minimum 7.2 mg. and the average 10 mg. of calcium per hundred c.c. of plasma.

Howland and Marriott [4] found that the calcium per hundred c.c. of serum was between 10 and 11 mg. in five normal infants.

It would seem useless to attempt to discuss separately and in detail the results obtained on the very considerable number of pathologic conditions represented by the figures given in Table 1. We shall, therefore, confine our discussion to the findings in those conditions in which there is at least a theoretical possibility that some abnormality of calcium metabolism may exist.

In this group rickets and infantile tetany are, perhaps, the most important, although there seems to be a possibility that some abnormality may exist in pneumonia, nephritis and, perhaps, in certain conditions associated with delayed blood coagulation.

3. Denis, W.: J. Biol. Chem. **41**:363, 1920.
4. Howland and Marriott: Quart. J. M. **11**:10, 1918.

TABLE 1.—Calcium Per 100 C.c. Blood Plasma Showing the Variations

No.	Sex*	Age	Season	Diagnosis	Calcium per 100 C.c. Plasma, Mg.	Magnesium per 100 C.c. Plasma, Mg.
1	♀	1 yr.	Winter	Microcephalus, delayed mental development...	13.5	....
2	♂	4 mo.	Spring	Regulation of feeding...	12.9	1.00
2a	♂	1½ yr.	Winter	Lobar pneumonia...	12.1	....
3	♀	7½ mo.	Autumn	Pyelitis...	11.6	....
4	♂	7½ yr.	Summer	Bronchopneumonia, foreign body in ear...	11.3	....
5	♂	10 mo.	Summer	Scurvy...	11.2	....
6	♂	3 mo.	Autumn	Regulation of feeding (artificial mixed)...	10.8	....
7	♂	11 mo.	Spring	Bronchopneumonia, colitis...	10.6	1.20
8	♂	3 mo.	Summer	Necrosis of alveolar process of right maxilla...	10.5	....
9	♂	21 mo.	Summer	Indigestion with fermentation...	10.4	....
10	♀	3 yr.	Winter	Hypertrophied tonsils and adenoids, cervical adenitis...	10.4	....
11	♀	10 yr.	Summer	Purpura hemorrhagica, chronic...	10.2	....
12	♀	7 mo.	Spring	Pharyngitis; retropharyngeal abscess; cervical adenitis; otitis media; congenital heart; rickets; secondary anemia...	10.1	2.20
12a	♀	7 mo.	Spring	Same as above...	10.1	2.20
13	♀	4 yr.	Summer	Sarcoma of kidney...	10.0	....
14	♂	2 mo.	Autumn	Regulation of feeding (breast)...	10.0	....
15	♀	3½ yr.	Winter	Retarded mental and physical development as result of previous encephalitis...	9.9	....
16	♀	4 mo.	Winter	Regulation of feeding, nephritis...	9.8	1.2
17	♂	6 yr.	Summer	Hydrocephalus decompression...	9.7	....
18	♀	7 mo.	Autumn	Microcephalus: hare lip: convulsions (?)...	9.7	....
19	♀	10 mo.	Spring	Lobar pneumonia...	9.7	....
20	♂	1 yr.	Winter	Bronchitis; cleft palate: hare lip...	9.6	2.0
21	♂	3 mo.	Summer	Regulation of feeding...	9.6	....
22	♀	9 mo.	Winter	Scurvy...	9.6	....
23	♂	6 yr.	Summer	Lobar pneumonia...	9.6	....
24	♀	10 mo.	Summer	Feeding; indigestion. carbohydrate; impetigo contagiosa...	9.4	....
25	♂	?	Summer	......	9.3	....
26	♂	2 yr	Autumn	Epilepsy; retarded mental development...	9.2	....
27	♀	16 mo.	Summer	Unresolved pneumonia; Tb. bronchial lymph nodes (+ von Pirquet); adenoids; rickets; congenital syphilis ?...	9.1	....
28	♂	5 yr.	Winter	Neoplasm of lung; died Nov. 7, 1919..	9.1	....
29	♀	2½ yr.	Summer	Infectious diarrhea...	8.8	....
30	♀	6½ mo.	Autumn	Acute fermental diarrhea; cellulitis scalp...	8.8	....
30a	♀	7 mo.	Autumn	Same as above...	8.8	....
32	♂	2¼ yr.	Summer	Bronchial glands; rickets...	8.8	....
33	♀	11 mo.	Winter	Amaurotic family idiocy...	8.8	....
34	♂	23 mo.	Winter	Foreign body in left bronchus; atelectasis...	8.6	....
35	♀	6 mo.	Spring	Regulation of feeding...	8.5	2.58
36	♀	8 yr.	Winter	Laryngismus stridulus (thymic asthma)...	8.4	....
37	♀	11 mo.	Summer	Congenital syphilis; otitis media; cerical adenitis; died Aug. 28 1919	8.4	....
38	♀	6 mo.	Spring	Regulation of feeding, same as No. 35	8.3	2.55
39	♀	6 yr.	Winter	Catarrhal jaundice...	8.3	....
40	♂	4 mo.	Winter	Regulation of feeding...	8.2	....
40a	♂	3 mo.	Spring	Convulsions (?) of cerebral or intestinal origin...	8.2	....
41	♂	4 mo.	Spring	Regulation of feeding...	8.1	1.6
42	♀	10 mo.	Spring	Rickets; bronchopneumonia (?); enlarged thymus; clubbed fingers...	8.0	1.60
43	♂	3 wk.	Winter	Congenital stenosis of pylorus...	8.0	....
44	♂	7 mo.	Summer	Regulation feeding; pylorospasm...	8.0	....
45	♀	8 mo.	Autumn	Intestinal indigestion due to carbohydrate...	8.0	....
46	♂	9 mo.	Autumn	Rumination; intestinal indigestion due to starch...	8.0	....
47	♂	6 yr.	Winter	Catarrhal jaundice...	8.0	....

* In this column, ♂ indicates male, and ♀ female.

TABLE 1.—Calcium Per 100 C.c. Blood Plasma Showing
the Variations—(*Continued*)

No.	Sex	Age	Season	Diagnosis	Calcium per 100 C.c. Plasma, Mg.	Magnesium per 100 C.c. Plasma, Mg.
48	♀	14 mo.	Autumn	Regulation of feeding (artificial).....	8.0	....
49	♂	6 yr.	Autumn	Tb. meningitis, cerebral; died Sept. 22, 1919.	8.0	....
50	♀	4 mo.	Winter	Chronic intestinal indigestion due to sugar malnutrition................	7.9	....
51	♀	15 mo.	Winter	Bronchitis (?); lobar pneumonia.....	7.7	2.0
52	♂	11 mo.	Autumn	Rickets; spasmophilia (?)............	7.7	....
53	♂	1 yr.	Winter	Acute bronchitis....................	7.7	....
			2 da. later	Acute bronchitis....................	7.7	....
54	♀	2 yr.	Winter	Bronchopneumonia...................	7.6	....
55	♀	22 mo.	Summer	Pyopneumothorax; pyelitis..........	7.6	....
55a	♂	7 yr.	Summer	Mitral insufficiency and stenosis; abrasion on chin..................	7.6	....
56	♀	3½ mo.	Winter	Chronic intestinal indigestion due to sugar malnutrition (see No. 50).....	7.4	....
57	♂	8 mo.	Winter	Regulation of feeding; bronchopneumonia; congenital syphilis..........	7.3	3.2
58	♂	1 yr.	Summer	Rickets; regulation of feeding........	7.2	1.27
59	♀	1 yr.	Summer	Splenomegaly; secondary anemia......	7.2	....
60	♂	14 mo.	Winter	Diarrhea; acute otitis media; bronchopneumonia......................	7.2	....
61	♂	17 mo.	Winter	Lobar pneumonia....................	7.2	....
62	♂	5½ yr.	Winter	Acute nephritis; follicular tonsillitis; cervical adenitis, chronic............	7.1	....
63	♀	6 wk.	Summer	Amaurotic idiocy (?); convulsions; regulation feeding..................	6.9	0.8
64	♀	10 mo.	Winter	Chronic intestinal indigestion........	6.9	....
65	♀	9 mo.	Winter	Bronchopneumonia (?); tuberculosis; tetany....................	6.8	2.0
66	♀	9 yr.	Summer	Migraine; eyestrain..................	6.8	....
67	♀	7 yr.	.Autumn	Progressive degeneration of cerebellum...........................	6.6	....
68	♂	4 yr.	Autumn	Hypernephroma with metastasis....	6.6	....
69	♀	5 yr.	Winter	Acute bronchitis....................	6.6	....
70	♀	4 yr.	Summer	Purpura............................	6.5	0.96
71	♂	3 yr.	Winter	Influenza; rickets; strabismus.......	6.5	2.7
72	♂	2 yr.	Summer	Measles; bronchopneumonia; morbilli..............................	6.4	....
73	♂	3 yr.	Summer	Acute meningitis; optic atrophy; hypopituitarism...................	6.4	....
74	♀	5 yr.	Autumn	Influenza; bronchopneumonia (?); meningismus; died Sept. 23, 1919....	6.4	....
75	♂	3½ yr.	Summer	Encephalitis.......................	6.3	1.60
76	♀	3 mo.	Winter	Regulation of feeding (artificial mixed)............................	6.3	....
77	♀	2 yr.	Winter	Otitis media (acute suppurative); rickets............................	6.3	....
78	♀	7 mo.	Winter	Influenza; bronchopneumonia.......	6.1	1.6
79	♀	11 mo.	Spring	Resolving bronchopneumonia (rachitis).............................	6.1	....
80	♂	29 mo.	Winter	Bronchopneumonia; congenital syphilis; rickets; iodid rash........	6.1	....
81	♀	9 mo.	Summer	Bronchopneumonia; pyelitis..........	6.1	....
82	♀	5 mo.	?	Tb. meningitis; miliary tuberculosis; dead..............................	6.0	....
82a	♀	22 mo.	Spring	Laryngismus stridulus...............	6.0	....
83	♂	5 yr.	Summer	Acute rheumatic fever; tonsillitis.....	6.0	....
83a	♂	10 mo.	?	Chronic meningitis..................	6.0	....
84	♂	8 yr.	Summer	Hypertrophied tonsils and adenoids; chorea; tonsillectomy.......	6.0	....
85	♂	21 mo.	Spring	Tuberculosis; peritonitis.............	5.8	2.55
86	♂	4 mo.	Summer	Regulation of feeding................	5.6	1.29
87	♂	11 mo.	Winter	Regulation of feeding (artificial mixed); pyelitis (?).................	5.5	....
88	♂	3 yr.	Winter	Epilepsy...........................	5.5	....
89	♀	7 yr.	Summer	Purpura; furunculosis, multiple......	5.3	1.20
90	♀	8 mo.	Winter	Convulsions; bronchopneumonia; impetigo; secondary anemia; rickets	5.3	0.80
91	♂	9 mo.	Winter	Regulation of feeding (artificial mixed); indigestion due to sugar...	5.2	....
92	♂	10 mo.	Winter	Hypertrophied tonsils and adenoids; spasmophilia (tetany).......	5.2	....
93	♂	8 yr.	Autumn	Acute lymphatic leukemia...........	5.2	....

TABLE 1.—Calcium Per 100 C.c. Blood Plasma Showing
the Variations—(*Continued*)

No.	Sex	Age	Season	Diagnosis	Calcium per 100 C.c. Plasma, Mg.	Magnesium per 100 C.c. Plasma, Mg.
94	♂	6 wk.	Summer	Birth injury (intracranial); broncho-pneumonia; died Aug. 21, 1919......	5.1	....
95	♂	6 mo.	Spring	B r o n c h i t i s; bronchopneumonia (acute intestinal indigestion).......	5.0	5.0
96	♀	17 mo.	Summer	Lobar pneumonia; pyelitis; empyema (progressive).................	5.0	1.55
97	♀	4 yr.	Spring	Epilepsy..............................	5.0	1.0
98	♂	2 yr.	Winter	Congenital heart; ulcerative stomatitis................................	5.0	....
99	♂	23 mo.	Summer	Intestinal indigestion......	4 8	....
100	♂	7 yr.	Summer	Chorea...............................	4.8	1.28
101	♂	10 mo.	Winter	Paralysis of 7th, 12th and 10th cranial nerves; miliary tuberculosis	4.7	2.4
102	♂?	3 mo.	Spring	Nasopharyngitis (?); (enlarged thymus)................................	4.6	2.5
103	♂	4 yr.	Summer	Empyema.............................	4.5	....
104	♂	5 yr.	Autumn	Lobar pneumonia....................	4.4	....
105	♂	4 mo.	Spring	Regulation of feeding; pylorospasm	3.8	....
106	♂	4½ mo.	Autumn	Chronic infectious diarrhea.........	3.4	....
107	♀	6 mo.	Winter	Influenza; bronchitis; reflex convulsions; died......................	3.2	....
108	♂	4 mo.	Spring	Regulation of feeding....,..........	3.1	1.00
109	♂	5 yr.	Summer	Petit mal............................	3.0	1.60
110	♂	5 mo.	Winter	Regulation of feeding; tetany.......	2.9	0.48
111	♂	7 mo.	Spring?	Rickets; tetany; laryngospasm; died in an attack.....................	2.5	1.28
112	♂	5 mo.	Winter	Convulsions; regulation of feeding; tetany................................	2.5	1.0
113	♂	5 mo.	Winter	Same as above.......................	2.0	1.0
114	♂	10 mo.	Spring	Bronchopneumonia; tuberculosis (?); rachitis; dead.................	<2.0	3.2
115	♂	10 mo.	Summer	Rachitis; regulation of feeding; tetany (?); microcephalus..........	+1.00	1.29
116	♂	4 mo.	Summer	Regulation of feeding...............	+1.00	1.29

TABLE 2.—Distribution of Calcium in Various Cases

Mg. of Calcium per 100 C.c. Blood Plasma	Number of Cases	Per Cent. of Total
13.5–12..	3	2.5
12 –10..	11	9.1
10 – 8..	29	24.2
8 – 6..	42	35.0
6 – 4..	23	19.2
4 – 1..	12	10.0

In Table 2 are presented the results obtained on the blood of 28 cases of rickets, seven in the acute and twenty-one in the convalescent stage. While in some of these cases the calcium values are distinctly below normal, the interpretation of the results is somewhat complicated by the fact that several of the patients whose blood gave low calcium values were also suffering from other maladies (pneumonia predominating), which might also affect the calcium level in the blood. No conclusions can, therefore, be drawn from these figures because, as will appear in a later table, changes are found in the blood in many cases of pneumonia.

TABLE 3.—CALCIUM PER 100 C.c. BLOOD PLASMA IN CASES WITH RICKETS

Acute Stage

No	Sex*	Age	Diagnosis	Epiphyses	Rosary	Mg. Calcium per 100 C.c.	Mg. Magnesium per 100 C.c.
114	♂	10 mo.	Rickets; bronchopneumonia....	Slight +	Marked +	<2.0	3.2
101	♂	10 mo.	Rickets; miliary tuberculosis...	Slight +	Moderate +	4.7	2 4
90	♀	8 mo.	Rickets; convulsions; broncho-pneumonia	+	Moderate +	5.3	0.8
82	♀	5 mo.	Miliary tuberculosis; rickets....	Slight +	Marked +	6.0	...
79	♀	11 mo.	Bronchopneumonia; rickets....	Moderate +	Marked +	6.1	...
58	♂	12 mo.	Rickets..................	Slight +	Well marked	7.2	1.27
42	♀	10 mo.	Rickets; bronchopneumonia....	Large	Marked	8 0	1.60

Convalescent Stage

No	Sex	Age	Diagnosis	Epiphyses	Rosary	Mg. Calcium per 100 C.c.	Mg. Magnesium per 100 C.c.
103	♂	4 yr.	Empyema........................	0	Slight +	4.5	...
99	♂	23 mo.	Intestinal indigestion...........	0	Slight +	4.8	...
95	♂	6 mo.	Bronchopneumonia.............	0	Slight +	5.0	5.0
85	♂	21 mo.	Tuberculous peritonitis.........	0	Slight +	5.8	2.55
83	♂	5 yr.	Acute rheumatism..............	0	Slight +	6 0	...
81	♀	9 mo.	Bronchopneumonia.............	0	Slight +	.6.1	...
77	♀	2 yr.	Otitis media....................	+	+	6 3	...
72	♂	2 yr.	Bronchopneumonia.............	Slight +	Slight +	6.4	...
71	♂	3 yr.	Influenza......................	Slight +	Moderate +	6.5	2 7
68	♂	4 yr.	Hypernephroma................	0	Prominent	6.6	...
57	♂	8 mo.	Congenital syphilis; broncho-pneumonia...................	0	Moderate +	7.3	3.2
55	♀	22 mo.	Pyelitis; pneumothorax........	Slight +	Slight +	7.6	...
35	♀	6 mo.	Regulation feeding.............	Slight +	Sl'ght +	8 3, 8.5	2.55, 2.58
32	♂	2¼ yr.	Enlarged bronchial glands......	Slight +	Slight +	8.8	...
30	♀	6½ mo.	Fermental diarrhea.............	0	Sl'ght +	8.8	...
29	♀	2½ yr.	Infectious diarrhea.............	0	Slight +	8.8	...
27	♀	16 mo.	Tuberculous bronchial glands..	0	Slight +	9.1	...
24	♀	10 mo.	Indigestion....................	Moderate +	Moderate +	9.4	...
22	♀	9 mo.	Scurvy........................	0	Def. +	9 6	...
12	♀	7 mo.	Otitis media; secondary anemia	Slight +	Slight +	10.1	2.2
5	♂	10 mo.	Scurvy........................	0	Marked +	11.2	...

* In this column, ♂ indicates male, and ♀ female.

TABLE 4.—CALCIUM PER 100 C.c. BLOOD PLASMA IN CASES OF TETANY

No.	Sex*	Age	Diagnosis	Mg. Calcium per 100 C.c.	Mg. Magnesium per 100 C.c.	Remarks
116	♂	4 mo.	Acute tetany...................	+1.00	1.29	
115	♂	10 mo.	Acute tetany; rickets; microcephalus	+1.00	1.29	
112	♂	5 mo.	Acute tetany; convulsions........	2.5	1.0	
113	♂	5 mo.	Acute tetany; convulsions........	2.0	1.0	Same as No. 112 after 13 days treatment
111	♂	7 mo.	Acute tetany with laryngospasm.....	2.5	1.28	Died in attack
110	♂	5 mo.	Acute tetany...................	2.9	0.48	
108	♂	4 mo.	During treatment and convalescence.	3.1	1.00	Same as No. 116. 5 and 19 days after calcium treatment
86	♂	4 mo.	During treatment and convalescence.	5 6	1.29	Same as No. 108
92	♂	10 mo.	Subacute tetany................	5.2	...	
65	♀	9 mo.	Subacute tetany................	6.8	2.00	
52	♀	11 mo.	Subacute tetany................	7.7	...	
82a	♀	22 mo.	Laryngismus stridulus..........	6.0	...	

* In this column, ♂ indicates male, and ♀ female.

In Table 4 are collected the results of our observations in ten cases of infantile tetany, and in Table 5 are detailed the results obtained on patients with convulsions, but without evidence of the presence of tetany. A diagnosis of tetany was made in our cases when carpopedal spasm, Chvosteck and Trousseau signs were present. This was confirmed in most of the cases by a lowered threshold of electric irritability.

TABLE 5.—Calcium Per 100 C.c. of Blood Plasma in Cases Having Convulsions without Evidence of Tetany

No.	Sex*	Age	Convulsions Without Evidence of Tetany	Mg. Calcium per 100 C.c.	Mg. Magnesium per 100 C.c.
107	♀	6 mo.	Reflex convulsions; influenza; bronchitis..............	3.2	...
90	♀	8 mo.	Convulsions; bronchopneumonia.....................	5 3	0.8
40a	♂	3 mo.	Convulsions of cerebral origin (?); intestinal (?)......	8.2	...
83a	♂	10 mo.	Chronic meningitis................................	6.0	...
			Epilepsy		
109	♂	5 yr.	Petit mal..	3.0	1.6
97	♀	4 yr.	Epilepsy..	5.0	1.0
88	♂	3 yr.	Epilepsy..	5.5	...
26	♂	2 yr.	Epilepsy, retarded mental development................	9.2	...
			Chorea		
100	♂	7 yr.	Chorea.................................:....	4.8	1.28
84	♂	8 yr.	Chorea; tonsils and adenoids.........................	6.0	....

* In this column, ♂ indicates male, and ♀ female.

In some of the cases in Table 4 the content of calcium in the serum is extremely low, while in a few of the more chronic cases it approaches normal values.

These figures are much lower than those of Howland and Marriott,[4] who found in active tetany an average of 5.6 mg., the lowest figure being 3.5 mg.

Calcium chlorid, 25 grains, three times daily were given in two cases of tetany and an increase in the blood calcium resulted which in one case (Cases 116, 108 and 84), was very marked. Associated with this increase of the calcium in the blood serum was the disappearance of symptoms and apparently complete cure. Denis and Minot[5] recently published the results of experiments on the administration of calcium by mouth to men, cats and rabbits. The results of this work indicate that in most cases it is impossible to increase the concentration of calcium in the plasma by ingestion of calcium salts, but that in cats and rabbits where the initial concentration is low, it is sometimes possible to greatly increase the amount of calcium in the plasma by feeding calcium salts.

5. Denis and Minot: J. Biol. Chem. **41**:357, 1920.

Our cases of convulsions not due to tetany (Table 5) showed, on the whole, lower figures than those found by Howland and Marriott. This was particularly noticeable in the cases with epilepsy in which three out of four cases showed less than 6 mg., while none of their cases showed less than 8.9 mg.

TABLE 6.—Calcium and Magnesium Per 100 C.c. Plasma in Lobar Pneumonia, Bronchopneumonia and Acute Bronchitis

No.	Sex*	Age	Diagnosis	Mg. Calcium per 100 C.c.	Mg. Magnesium per 100 C.c.	Temperature, F.	Duration of Pneumonia
2a	♂	1½ yr.	Lobar pneumonia.........................	12.1	...	99-100	After crisis
19	♀	10 mo.	Lobar pneumonia.........................	9.7	...	101-105	4 days
23	♂	6 yr.	Lobar pneumonia.........................	9.6	...	106	8 days
61	♂	17 mo.	Lobar pneumonia.........................	7.2	...	98.6	2 da. after crisis
96	♀	17 mo.	Lobar pneumonia.........................	5.0	1.55	106	2 weeks
104	♂	5 yr.	Lobar pneumonia.........................	4.4	...	103	6 days
4	♂	7½ yr.	Bronchopneumonia....................	11.3	...	99	2 weeks
7	♂	11 mo.	Bronchopneumonia....................	10.6	1.2	103	13 days
42	♀	10 mo.	Bronchopneumonia; rickets.............	8.0	1.6	101	Weeks ?
54	♀	2 yr.	Bronchopneumonia....................	7.6	...	104-98.6	7+ days
57	♂	8 mo.	Bronchopneumonia; congenital syphilis..	7.3	3.2	102	5 days
60	♂	14 mo.	Bronchopneumonia; diarrhea...........	7.2	...	102	3 days
65	♀	9 mo.	Bronchopneumonia....................	6.8	2.0	103	20 days
72	♂	2 yr.	Bronchopneumonia; measles............	6.4	...	102	4-5 days
78	♀	7 mo.	Bronchopneumonia; influenza...........	6.1	1.6	104	10 days
79	♀	11 mo.	Bronchopneumonia; rickets.............	6.1	...	99	
80	♂	29 mo.	Bronchopneumonia; rickets.............	6.1	...	101-103	4 days
81	♀	9 mo.	Bronchopneumonia; rickets.............	6.1	...	99	8-10 days
90	♀	8 mo.	Bronchopneumonia; rickets; convulsions	5.3	0.8	99-103	
95	♂	6 mo.	Bronchopneumonia; rickets.............	5.0	5.0	105-100	4 days
114	♂	10 mo.	Bronchopneumonia; rickets; died........	<2.0	3.2	103	4 days
51	♀	15 mo.	Acute bronchitis; ? lobar pneumonia.....	7.7	2.0	99	
53	♂	1 yr.	Acute bronchitis.........................	7.7	...	99	
69	♀	5 yr.	Acute bronchitis.........................	6.6	...	99-100	

* In this column, ♂ indicates male, and ♀ female.

In Table 6 we have collected the results obtained in twenty-five cases including lobar pneumonia, bronchopneumonia and acute bronchitis. Here, again, some very low figures were obtained. That the calcium content of the blood in pneumonia may be diminished has been suggested by the work of von Moraczewski [6] and Peabody,[7] At the time that these earlier works were done the large amounts of blood required for the analysis prevented the collection of any considerable amount of data so that in the opinion of investigators themselves the findings are more suggestive than definite. Peabody's findings are especially suggestive because he found that during pneumonia there was a calcium retention and after the crisis there was calcium excreted from the body. The blood calcium during the fever, however, was lower than the blood calcium after the crisis. In our cases there was no definite relation between the fever and the amount of

6. von Moraczewski: Virchows Arch. f. Path. Anat. **155:** 1899.
7. Peabody: J. Exper. M. **17:**71, 1913.

blood calcium found in bronchopneumonia. In lobar pneumonia, the figures are also inconclusive but there is a tendency for the blood calcium to be higher after the crisis.

SUMMARY

As the result of a series of observations of the calcium and magnesium content of the blood of 119 children, we have found that a low calcium content of the serum frequently occurs in infantile tetany, acute rickets and in pneumonia. In one case of tetany there was a considerable increase in the blood calcium after the administration of calcium chlorid by mouth. Several cases of epilepsy had a low blood calcium; the significance of these findings is as yet uncertain.

THE ULCERATED MEATUS IN THE CIRCUMCISED CHILD *

JOSEPH BRENNEMANN, M.D.

CHICAGO

For a number of years my attention has been drawn with increasing frequency to a peculiar lesion of the meatus urinarius occurring only in circumcised male children, and characterized by ulceration, crusting, narrowing of the urinary passage, and nearly always accompanied by painful urination, often with distended bladder, and, occasionally, by hemorrhages. I have been able to find only one reference [1] to it in the literature. While this condition probably is common in occurrence in the experience of all pediatrists, I am inclined to believe that it is more common in this locality and in more recent years than in some other localities and in my own earlier years, and that the manifestations are more severe.

My first impression was that this lesion was caused by rubbing against the clothing of the naturally most accessible and most vulnerable portion of the exposed glans, the meatus. This, however, seemed improbable, for it would hardly explain the deep ulceration often seen, and it was soon evident that similar lesions about the diaper region were not infrequently present at the same time. For a time attention was directed to the narrowness of the meatus as a possible cause, though we soon learned that in doing so we were looking for a cause in what was in reality an effect. Routine examination of the urine gave us no help. Only in the last year or two has the real explanation become increasingly evident. In the twenty-five or more cases seen during the past winter and spring there has been no exception to the observation that this lesion is associated with what is known as the ammoniacal diaper. I had not been aware that anyone had ever reached a similar conclusion, but on looking over Zahorsky's paper [1] on the ammoniacal diaper again I found that he had devoted a paragraph to an excellent description of the lesion in question and had also traced its origin to the ammoniacal diaper. So far as I know this is the only reference to this association in the literature.

While the condition itself is rarely, if ever, of serious import, it is nevertheless usually very troublesome and the apparent general lack of knowledge of its pathogenesis would seem to warrant its presenta-

tion. Its peculiar location, moreover, always causes deep concern in the household.

More commonly the lesion manifests itself as a rather superficial ulceration about the meatus. From what we know about the development of similar ulcers in the diaper region due to the same cause it is probably preceded, as pointed out by Zahorsky,[1] by a vesicle, though this is rarely seen before it is broken. At times the ulcer becomes deep and extensive, up to 2 mm. in depth and more than 5 mm. in width. Usually it is more or less covered by a crust which is very firmly attached over a considerable area. Surrounding the ulcer there is often an area of inflammation which involves both the adjacent surface of the glans and extends into the urethral opening with consequent narrowing. In the severer cases there are commonly present at the same time erythema, vesication and ulceration of the glans, scrotum and the rest of the diaper region wherever the diaper is in intimate contact with the skin.

SYMPTOMS

The symptomatology is evident from the pathology. The salty urine coming in contact with the denuded meatus causes acute. pain when the child begins to urinate. He immediately stops urinating and cries with pain. A subsequent attempt to urinate, as the discomfort from a distended bladder forces him to try it again, leads to the same result. No amount of coaxing will induce him to try it again until the distended bladder becomes intolerable or begins to overflow. Then, having once started, the grateful relief that comes from emptying the bladder and the lessening of the pain of the first contact with the urine, will cause him to continue to urinate until the bladder is more or less emptied. Unless the condition is quickly remedied the same cycle repeats itself at the next urination. Often the emptying of the bladder is deferred for from twelve to eighteen hours. As a rule, the condition is less severe than that just described, and the child will urinate before there is very painful distention.

In some cases there is a greater or lesser degree of mechanical obstruction. The urethral opening is nearly always narrowed, often so much so that the urinary stream is threadlike and the urine can be expelled only with evident effort. I have never seen this alone cause serious obstruction. A more frequent cause of nearly complete obstruction is the scab that forms on the ulcerated area. This is very adherent and can hardly be removed without tearing and bleeding of the denuded and adjacent portion of the glans. This is practically always accompanied by a narrowing of the meatus, and it is at times impossible to tell whether the occlusion is due chiefly to the scab or to the narrowing of the urethra itself. Two cases that recently came under observation illustrate these points.

REPORT OF CASES

CASE 1.—A child, aged 2 years, was unable to empty the bladder both because of pain and obstruction and because of overdistention of the bladder. From time to time, there was a dribbling overflow that found considerable difficulty in making its exit. In spite of desperate efforts, aided by coaxing from his mother, he was able only intermittently to force out to a height of two feet two tiny divergent streams no thicker than a fine thread.

Examination showed the meatus completely covered with a firm, dry, parchment-like crust that almost completely occluded the opening, and so firmly adherent that it did not seem expedient to remove it at the time. The bladder was distended almost to the umbilicus. By continuous, gentle pressure over the bladder, and with much coaxing to voluntary effort, we were finally able to empty it almost completely through the two minute openings. If pressure over the bladder was stopped for a moment, the flow would stop immediately as if the bladder had been paralyzed by the overdistention.

CASE 2.—A boy, aged 2½ years, was apparently unable to empty the bladder, probably both because of pain and of great narrowing of the meatus. The opening was barely visible, being so small that it would hardly have admitted a fine needle. The meatus itself was apparently narrowed to this degree and was further covered by a tough skinlike crust that had to be removed, but only at the expense of considerable pain and some blood and adjacent epidermis. Even then the meatus could barely be made out, and it was difficult to see how the bladder could be emptied through it.

A permanent narrowing of the meatus, analogous to a stricture, apparently never occurs even after repeated and prolonged ulceration. In the two cases just cited, after appropriate treatment, the urinary stream was apparently of normal caliber on the following day. The restoration to a normal condition is commonly as rapid as the original production of the lesion itself.

One other symptom occasionally causes great concern to the mother but is never serious. If the ulceration is deep and extensive, there is, at times, a little hemorrhage especially noticed at the end of urination. It is surprising that this does not happen oftener when one considers the great vascularity of the glans.

The ammoniacal diaper that apparently always causes this condition of the meatus is to me still surrounded with mystery in spite of its common occurrence. Clinically it manifests itself as follows. An infant or young child that has, perhaps, attracted no attention to its general health or its state of nutrition, or digestion, except that it is constipated, is noticed when changed at night or in the morning, to have a very strong odor of ammonia about the wet diaper. This odor is not simply one detectable on close effort. The fumes are comparable to those that escape from a bottle of ammonia. They are distinctly irritating to the nostrils, and even cause a biting sensation in the eyes as one stoops over the open diaper. This condition is rarely noticed, except at night and most often toward morning. If the urine of such a child voided later is allowed to stand in a vessel no odor of ammonia is detectable even if it is kept at body temperature.

Sometimes, the condition is present every night, continuously and consecutively, as in a case I saw recently, for over a year. Again, it is apparently absent, or barely noticeable, for weeks and months, only to appear again without any known change in health or in food, with violent manifestations. In one of my own children during the second year the condition would occasionally appear in mild form, then be absent for weeks or months. Suddenly at night, without premonition, or any known provocation, the child would wake up toward morning screaming with pain, the diaper would be almost intolerably strong of ammonia, and the whole diaper region would be reddened and painful as if scalded, and covered with blisters. In a day or so without any treatment the condition would disappear as mysteriously as it came, only to reappear at a subsequent time, perhaps for a longer stay. The condition is apparently much more frequent in private homes than in hospital wards.

Many children have this ammoniacal diaper for weeks and months without any other unpleasant symptoms. Usually it produces at least a local redness and subsequent desquamation of a large part of the diaper region. In severer cases there is scattered vesication and ulceration. These ulcers often remain denuded for a long time, often they heal over but remain as discrete nodules during the whole time that the ammoniacal condition persists. Often the exposed meatus is the only seat of a deeper lesion; rarely it escapes; as a rule, it is involved with the rest of the diaper region.

For the production of skin lesions contact with the wet ammoniacal diaper is apparently always necessary. The word diaper is, of course, here used in a generic sense and includes any article of clothing, or bedding. The skin is always most irritated where the contact is most intimate and prolonged—over the buttocks and lower back, from lying, and across the abdomen and about the thighs above the knees, because of the tighter application of the diaper. The male meatus is peculiarly exposed to such contact, and the delicate mucous membrane is the most vulnerable spot; the female meatus is well protected and is apparently rarely if ever involved. The effect of contact was well illustrated in the first case cited above. For several nights the child did not wet the diaper and the ulcer healed. A few days later he was again unable to urinate because of a new ulceration of the meatus. Without any questioning the mother said that he had wet his underclothing over a small spot with urine and that contact with this spot had apparently brought the trouble on again. The favorable effect that follows dispensing with the diaper at night further confirms this view.

AGE INCIDENCE

The age incidence of this condition is of special interest. It is almost unknown in the nursing baby, though I have seen it in a baby on mixed feeding; is relatively rare in the first six months, and is only exceptionally encountered before the third or fourth month. It is much more common in the latter half of the first year; probably attains its maximum frequency and severity during the second year; becomes less common during the third year, and vanishes soon after this. The lesser incidence after the third year is probably due to the greater infrequency of bed wetting without which it would not be recognizable.

TREATMENT

The treatment of this condition naturally is directed to the lesion itself if it is present, and to the prophylaxis and treatment of the ammoniacal diaper.

If the meatus is ulcerated or crusted over to some extent, and there is no obstruction, the proper therapy would seem to consist in applying thickly some substance like petrolatum that would coat over the involved area so that urination may be less painful and so that there will be protection on contact with the diaper. When the meatus is acutely inflamed, the opening narrowed and covered with an obstructing scab, and urination is difficult and peculiarly painful because of the inflammatory condition, a wet boric acid dressing has always quickly relieved the urgent indications. Gauze wet with the solution is fluffed over and about the penis, this is covered with a thick layer of cotton extending beyond the gauze to keep it in place, and over this the diaper is pinned snugly. The gauze is kept wet with the solution and is changed after each urination. The relief from this procedure has been unfailing and almost instantaneous. Dispensing with the diaper at night often has a favorable effect in preventing new lesions and in allowing old ones to heal. Mechanical dilatation has never been necessary. Neither has catheterization, which would be strongly contraindicated unless absolutely unavoidable.

If the scab itself is causing obstruction, or if it can be removed without injury to the adjacent tissues, this should be done. This is facilitated by the previous application of petrolatum or a wet dressing.

The cautious application of a very weak solution of cocain to the ulcerated area in case the child will not urinate because of pain would seem rational and unobjectionable, though the remembrance of a former attempt to urinate might lessen its usefulness.

The prophylaxis of the ammoniacal diaper presupposes a knowledge of its pathogenesis. To my mind we do not possess this knowledge at the present time with complete clarity.

The more inviting theory is that based on the work of Keller and others that in certain nutritional disturbances due to the ingestion of cow's milk fat beyond the infant's tolerance there is produced a relative acidosis of enteric origin which manifests itself in the urine in the excretion of a hypernormal amount of ammonium salts. This view has been formally championed by Southworth,[2] who reported a number of cases presenting this clinical picture and the patients were relieved of this symptom when the fat was reduced to an adequate degree. He also reported a similar result from the administration of alkalies, favoring potassium, calcium and magnesium bases over those of sodium. The cases detailed by Southworth were nearly all in younger infants in whom there was a definite clinical picture of overfeeding with fat or with milk and the therapeutic results would seem to leave little doubt as to the nature of the primary condition that produced the ammoniacal diaper in these cases.

I am inclined to believe that this explanation may be accepted as one factor in the case of younger infants fed exclusively on the bottle. This might further explain the greater frequency of this condition in my own cases for it has been my practice in recent years to give relatively more milk and less carbohydrate in the bottle feedings than formerly. In fact, the condition has been so frequent in my own cases that I have even assumed it to be within the range of normal and have used no measures to relieve it unless there was definite skin irritation. Even in these cases, however, where a dietetic relationship seems most evident I have been struck by the frequency with which neither reduction of the fat by lessening the milk or by taking off the cream nor the use of alkalies leads to an appreciable therapeutic result.

It seems to me, however, quite impossible on this hypothesis alone to explain the occurrence of the ammoniacal diaper in a very large number of cases. It is, for example, a well known fact that the ammoniacal diaper occurs with greater regularity when dried milk is used than with almost any other food. In my own experience, the severer manifestations, such as vesication and ulceration, occur more frequently in older children who are on a liberal diet and are getting very little milk. One of the most severe and protracted cases I have seen with extensive ulceration of the meatus, scrotum, and, in fact, of the whole diaper region, was in a child, aged $2\frac{1}{2}$ years, that was on a general diet and getting only a pint of skimmed milk. In some cases the mothers have stated that these older children were getting practically no milk at all. Cutting down the milk or removing the cream, even to a marked degree, has in the case of older children been

2. Southworth, T. S.: The Ammoniacal Diaper and Its Correction, Arch. Pediat. **30**:10 (Oct.) 1913.

quite disappointing from a therapeutic standpoint. The use of alkalies has given the same impression.

DISCUSSION

It is interesting in this connection to note that the ammoniacal diaper occurs less frequently and less severely with cream mixtures than with simple whole milk mixtures, or even, as has been pointed out, with dried skimmed milk mixtures. If this observation is correct, then the fat alone cannot account for the condition. This is further borne out by the relative freedom from this symptom when albumin milk is given in spite of its high fat content. It will be recalled that Czerny and Keller's "milchnährschaden," which is apparently due to an excess of fat in the infant's food and in which there is a heightened urinary excretion of ammonium salt, is produced when whole milk is fed in excess of tolerance. Certainly, it does not occur as definitely with cream mixtures, in spite of the fact that fat is assumed to be the factor that causes it. It will be recalled further that Czerny and Keller state that the soap stool does not occur with cream mixtures and they offer the ingenuous explanation that this is due to the fact that it is difficult to get cream that is not "zersetzt," that is, unfavorably influenced by bacteria.

To me it seems more reasonable that while the symptom under discussion may be due to the fat, at least in that class of cases where there is clinical evidence of overfeeding with fat, that fat will cause it only in certain combinations, and only if certain other food elements are represented in certain relative ratios to the fat. Thus, in a milk mixture it occurs less frequently if the fat is relatively higher than the protein and the salts as compared with their normal relative representation in whole milk; and more frequently if the normal proportion is maintained, or even if the fat is relatively lower than the protein and the salts. The fact is not sufficiently emphasized that the different food elements cannot be considered as isolated factors but must always be considered in relation to the other food elements in the causation of clinical pictures.

While the fat within these limitations may account for an increased excretion of ammonium salts in a certain proportion of these cases, and may thus supply one factor in the pathogenesis of the ammoniacal diaper, I do not believe that it accounts for all or most of them. Even in those cases where the fat would seem most clearly the causal agent, it is impossible to exclude the protein, or even the salts as a factor. I have gained the impression that, in the production both of the clinical picture of "milchnährschaden," and of the ammoniacal diaper, it is not so much a matter of amount of fat as of the amount of

milk even if it is partly skimmed. The protein and the salts, if this observation is correct, would command attention and especially, of course, the protein. This would explain many phenomena that cannot be accounted for on the assumption that the fat is the main factor. It would explain the frequency of the ammoniacal diaper when Dryco Milk is used in spite of its low fat content because as commonly used the amount of protein is relatively considerably higher than with ordinary fresh milk mixtures. Assuming that a milk from which two thirds of the fat has been removed is reduced to about one eighth or one ninth its volume in the process of desiccation, and that eight level tablespoonfuls of the dried product represent one ounce by weight, then one level tablespoonful would equal approximately one ounce of fresh milk, skimmed to a nearly equal extent. In giving two and one-half or even three tablespoonfuls of the dried milk to each pound of baby, as is commonly done, one would give the protein and salt equivalent of at least from 2½ to 3 ounces of milk to the pound of baby which would represent a much larger amount than is ever used in feeding fresh milk. This might also explain the greater frequency of the occurrence of the ammoniacal diaper in my own experience in more recent years during which I have been feeding more milk, that is, more protein and less carbohydrate. On this basis, too, one might find a satisfactory explanation for those cases in older children that are on a nearly general, almost fat free, diet.

The failure of ammonuria to occur, except in connection with the wet diaper in situ, together with the peculiar behavior of the ammoniacal diaper would suggest a further nondietetic factor residing in the diaper itself. A hyperexcretion of ammonium salts cannot alone be assumed to account for the ammoniacal diaper. We have here not combined but free ammonia. The ammonium salts that would be present in this condition are fairly stable, and it is very doubtful whether the evaporation of the urine would be carried to a point where ammonia would be liberated to the extent found in these diapers. It is well known that certain alkalies break up ammonium salts and liberate free ammonia. On this basis Zahorsky,[1] after failure to combat the condition by lessening the fat in the food and by the use of alkalies therapeutically, came to the conclusion that "the immediate cause of the ammoniacal diaper is the presence of an alkali in the diaper, or the bedding." This alkali he traced to "strong alkaline soap that had not been rinsed thoroughly from the diapers, or bedding, or to the presence of an alkaline stool, or to the possible presence of lime in the dried diaper in locations like St. Louis where the lime content of the water is high."

Zahorsky's explanation was distinctly appealing in that it alone, apparently, could account for the mysterious vagaries of the ammo-

niacal diaper; the startling appearance and sudden disappearance without known change in food or in health; the invariable association with the wet diaper in situ only; the failure of dietetic and alkaline treatment in many cases; and the greater incidence and severity of the symptom in older children which he also noted. Unfortunately he contented himself with saying: "It is not necessary to give the details" and presented no evidence. That soap, lime, and an alkaline stool do not explain the condition in a great many cases can easily be demonstrated by excluding these factors experimentally.

Other agents, however, may produce the same result and the action of bacteria naturally suggests itself. Thus in a recent personal communication Zahorsky says: "The diaper or the bedding, infected by an enormous number of bacteria, not boiled daily, must also be considered." The thought would suggest itself further that bacteria might liberate ammonia, not directly or indirectly from the ammonium salts in the urine, but from the urea. It is well known, for example, that *Micrococcus ureae*, and probably also other organisms in the urine, act on urea with the liberation of ammonia. As suggested by Kendall in a personal communication, the large evaporating surface presented by the diaper as compared with the small surface in the test tube would naturally lead to the freeing of a comparatively larger amount of ammonia. These considerations would lead us back again to the clinical impression already recorded that the determining factor in those cases in which the dietetic factors are easily grasped is the amount of milk given even if skimmed; that is, of protein, rather than, say, the amount of fat. More milk carries with it more protein and an increased excretion of urea for bacteria to act upon.

The further question would naturally arise whether a hyperexcretion of ammonium salts, or of urea, due to an excess of either the fat or the protein in the diet, is a prerequisite to the production of the ammoniacal diaper; or whether something in the diaper itself is sufficient to elicit the condition in a normal urine. So far as I know, the answer to this question is not yet at hand. The fact that free ammonia occurs with great regularity with certain foods, and an excessive amount of fresh milk such as Dryco milk, would point to the conclusion that the diaper alone is not sufficient to bring out this symptom unless there is an abnormal urinary condition. The occurrence in older children on a general diet makes it hard to assume an abnormal urinary factor and would suggest that the diaper can cause it even if the urine is normal. The invariable association of this symptom with the diaper would again suggest the diaper as the important factor and especially in these cases where the symptom occurs erratically. Some further observations made by Zahorsky are interesting but inconclusive in this connection. He found that "the ammo-

nia content of the urine was relatively higher in older children than in infants," and "while rather high in children presenting this symptom (ammoniacal diaper) not higher than in many who did not present it." He found further that "all but one of the patients so examined," that is, those having ammoniacal diapers, "showed the ammonia nitrogen higher in the morning after the night's rest." The fact that the ammoniacal diaper is rare in hospital cases as compared with those in private practice can be accounted for on either basis. In hospitals all diapers are thoroughly sterilized for obvious reasons, while in homes this is commonly omitted. On the other hand, it is also true that hospital babies, as a rule, can stand less milk than babies in private practice and so the dietetic factor is reduced to a minimum.

While our knowledge of the whole subject lacks precision and finality, nevertheless it gives us a definite line of treatment. The prophylaxis of the ammoniacal diaper and so of the ulcerated meatus, in accordance with our present state of knowledge, would consist then, in the avoidance of an excess of milk in the diet and a compensating use of the more tolerable carbohydrates, the dextrin-maltose preparations in younger infants, and these together with the starches in older infants. The treatment would consist in the reduction of the amount of milk; the increase, if permissible, of the carbohydrates; together with the use of such alkalies as milk of magnesia, lime water, or potassium salts. In selected cases malt soup best meets all of these indications. In older children on a general, nearly milk free diet, the dietetic treatment is still baffling in my own experience. The indications on the part of the diaper would be met by thorough rinsing and thorough boiling daily of all diapers and night clothes, possibly even the bedding.

The bearing of this lesion on the question of circumcision is perhaps evident.

· CONCLUSIONS

1. An ulcerated meatus in the circumcised child only is a frequent symptom.

2. The "ammoniacal diaper" is the cause of this lesion.

3. The etiology of the "ammoniacal diaper" is still obscure but seems due to one or both of two factors: a dietic error that increases the ammonium or urea content of the urine, and the presence of an alkali or of certain bacteria in the diaper.

4. The treatment consists in correcting, if possible, the dietetic error and in thorough rinsing and boiling of the diapers, night clothes and bedding.

A STUDY OF TUBERCULOSIS IN INFANTS AND YOUNG CHILDREN *

MARTHA WOLLSTEIN, M.D., AND RALPH C. SPENCE, M.D.

NEW YORK

From April 1, 1914 to April 1, 1920, 8,919 sick children were admitted to the Babies' Hospital. Among them were 359, or 4 per cent., who had symptoms of tuberculosis in some form; while three others had tuberculous lesions at necropsy which had not been suspected during life. In all then, 362 children with tuberculosis were admitted. During these six years 2,024 necropsies were performed, and 184, or 9 per cent., were on tuberculous subjects. By comparison with two previous studies,[1] in which respectively 13 and 16 per cent. of the children coming to necropsy were found to have tuberculosis, there has been an actual reduction in the number of children showing tuberculous lesions at necropsy during the past six years. That is, 184 of 2,024 necropsies showed tuberculosis in the years from 1914 to 1920, while from 1908 to 1914 there were 178 of 1,320 necropsies which disclosed tuberculous lesions. The number of children admitted with tuberculosis has decreased slightly, from 5.04 per cent. during the period of the first study (1898 to 1908), to 4.15 per cent. during the period of the second study (from 1908 to 1914), and again to 4.06 per cent. in the period from 1914 to 1920. At the same time, the total death rate for all admissions to the Babies' Hospital has decreased, while the death rate for cases of tuberculosis has increased. Since the percentage of necropsies permitted is greater at present than it was a decade ago, the decrease in the number of necropsies on tuberculous subjects, in spite of the higher death rate for tuberculosis, is significant.

From the figures of Table 1 it would seem that tuberculosis is slowly decreasing among the class of infants and young children in New York City from which the Babies' Hospital draws its admissions. The decrease may be ascribed to a combination of several factors, important among which are the education of mothers in the hygiene

---

1. Wollstein, M.: The Distribution of Tuberculous Lesions in Infants and Young children, Arch. Int. Med., **3**:221 (Feb.) 1909. Wollstein, M., and Bartlett, F. H.: A Study of Tuberculous Lesions in Infants and Young Children, Based on Postmortem Examinations. Am. J. Dis. Child. **8**:362 (Sept.) 1914.

of the infant and the home, and better provision for isolation and care of adults with tuberculosis, since the great majority of cases of infantile tuberculosis is caused by the human type of tubercle bacillus. While care of the milk supply is of gravest importance, the fact that only a small percentage of this country is infected with the bovine type of tubercle bacillus shows that it is not the prime factor in the reduction in the number of cases of tuberculosis which our studies show.

The curve of incidence of cases of tuberculosis plotted according to the month of admission, shows that the greatest number occurred from February to June inclusive, and the lowest number during the second half of the year. In comparing tuberculosis with the nontuberculous respiratory infections, it becomes apparent that the number of tuberculous patients increases as the respiratory infections subside
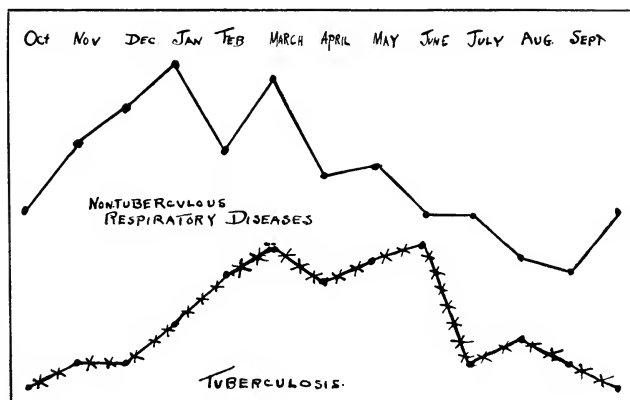
Comparison by months of admissions of cases of nontuberculous respiratory diseases with tuberculosis. The latter increase as the former lessen in number.

(see chart). The connection between the two is obvious. The general resistance of children who are exposed to tuberculosis is markedly diminished by an acute respiratory infection of whatever cause, especially if pneumonia occurs. In consequence, a latent tuberculous focus may become active, or an acute tuberculous infection may be acquired.

HISTORY OF EXPOSURE

A definite history of exposure was obtained for only ninety-four of 362 children in our series. There were twenty-nine tuberculous mothers; thirty-seven fathers had the disease; seven grandparents were the source of infection, while eight children contracted the disease from sisters and brothers, eleven from aunts and uncles, and two from friends. It is interesting to note that the youngest infants were infected by the mother. One child, aged 6 weeks, and two aged 8

weeks, were exposed to tuberculous mothers. Twenty-two of twenty-nine children whose mothers were tuberculous died before they were 1 year old; six died in the second year of life and only one boy was three years old at the time of his death. Fathers, on the contrary, come into less intimate contact with the young infants, and only sixteen of the thirty-seven whose fathers had tuberculosis died before they were one year old; eleven lived to be over 2 years old, while one reached the age of 5 years. The youngest infant who contracted tuberculosis from the father was 4 months old. Infection from other relatives occurred in only fourteen children under one year of age, or half of the twenty-eight so exposed.

TABLE 1.—INCIDENCE OF TUBERCULOSIS AS DIAGNOSED CLINICALLY AND AT NECROPSY

Time	Number of Admissions	Cases of Tuberculosis Admitted	Number of Necropsies	Cases of Tuberculosis Found at Necropsy	Death Rate for All Admissions, per Cent.	Death Rate for Tuberculosis Cases, per Cent.
1889 to 1908	9,165	462	1,131	185 or 16.4%	31.3	82.2
1908 to 1914	7,467	310	1,320	178 or 13.5%	32.2	86.8
1914 to 1920	8,919	362	2,024	184 or 9%	28.0	93.0

It must be remembered that a negative family history is of comparatively little value, and by no means always true.

AGE

In age the 362 children in our series ranged from 6 weeks to 5 years as follows:

TABLE 2.—INCIDENCE OF TUBERCULOSIS BY AGES

Under 3 months	3	
Between 3 and 6 months	41—	44 under 6 months, 12 per cent.
Between 6 and 12 months	95—139 under 1 year, 38 per cent.
Between 12 and 18 months	76	
Between 18 and 24 months	49—264 under 2 years, 73 per cent.
Between 2 and 3 years	46—310 under 3 years, 86 per cent.
Between 3 and 4 years	31	
Between 4 and 5 years	12	
Five years	9—	52 over 3 years, 14 per cent.

No case of congenital tuberculosis came under observation. Of the children admitted with tuberculosis 73 per cent. were under 2 years of age, and only 14 per cent. were over 3 years of age. The greatest frequency was noted in children between 6 and 12 months

old. Rabadeau-Dumas [2] found that the ages of 8 months and 2 years, respectively, supplied the largest number of cases of tuberculosis among young children.

<div align="center">RACE</div>

There were more tuberculous children of American parentage (155) admitted to the hospital than of any other one nationality. Sixty-four children were of Italian parentage; the parents of 36 were Irish, 34 were from Austria-Hungary; 30 from Russia; 14 were Germans; 7 English; 3 Spaniards and 3 Roumanians. The parents of 57 per cent. of these children were foreign born, and only 43 per cent. were born of Americans, including 12 per cent. who were negroes.

Without entering into a discussion of the value of the von Pirquet skin test, it may be remarked that 269 of the 362 children in the series, or 74 per cent., gave a positive reaction; fifty did not react, and in forty-three cases the reaction was not recorded.

Clinically, the cases were grouped as follows: 193 patients had tuberculous meningitis, 28 had tuberculous peritonitis, 116 had pulmonary and general miliary tuberculosis, 2 had intestinal tuberculosis without peritonitis, 10 had cervical adenitis, 12 had tuberculosis of the bones, and one infant had genital tuberculosis following circumcision. All but 24 of the children died, and 184 came to necropsy (Table 3). The nonfatal cases were those with tuberculosis of the fingers, knee, hip, vertebrae or cervical glands who were discharged from the hospital, and of which final outcome is unknown.

TABLE 3.—CLINICAL FORMS OF TUBERCULOSIS AMONG 362 CHILDREN ADMITTED
TO BABIES' HOSPITAL

	Cases
Tuberculous meningitis	193
Tuberculous peritonitis	28
Pulmonary and general miliary tuberculosis	116
Intestinal tuberculosis without peritonitis	2
Tuberculous cervical adenitis	10
Tuberculosis of the bones	12
Tuberculosis of penis and inguinal glands	1
Total	362

The necropsies include 123 cases of meningitis, five of peritonitis, fifty-four of pulmonary tuberculosis, and two cases of intestinal tuberculosis without peritonitis.

Grouping the necropsies according to the oldest lesion found in the body, we have classified the cases into those which were primary in the respiratory and digestive tracts, respectively. In several

---

2. Rabadeau-Dumas, L.: Tuberculosis in Children, Progrés. méd. **34**:312, 1919.

instances, the lesions seemed to be about the same age in both, so that it was impossible to group them with accuracy. One case of genital tuberculosis following circumcision did not come to necropsy.

TUBERCULOSIS PRIMARY IN THE RESPIRATORY TRACT

In some of these cases the oldest lesion was found in the lungs, in others in the bronchial glands, and in still others the lesions in the lungs and in the glands seemed to be about the same age. The first group, with the oldest lesion in the lungs, comprised seventy-four cases. Calcareous areas in the lungs were noted in only three instances. Cavities, usually of small size, were present in forty lungs examined, or in 21 per cent.

The primary lesion was found more often in the upper than in the lower lobes, and was present almost as frequently in the left upper (sixteen times) as in the right upper (seventeen times) lobe. It occurred in the right lower lobe thirteen times, in the left lower lobe sixteen times and in the right middle lobe eleven times. As in previous studies of cases in this hospital the right lung was found affected more frequently (forty-two times) than was the left (thirty-two times).

There was no instance in which the lung alone was the seat of a tuberculous lesion. In one case there was only a small tuberculous nodule with a calcareous center in the left upper lobe and a calcareous nodule in one bronchial lymph node. This occurred in a child 9 months old, who died of bronchopneumonia following diarrhea, without any clinical evidence of tuberculosis. Another child of 3 years had one small, tuberculous, cheesy nodule, surrounded by a few recent tubercles, in the left upper lobe, while several bronchial lymph nodes contained tubercles with cheesy centers. This child died of a simple bronchopneumonia. Tuberculosis was discovered at necropsy.

The bronchial glands contained the primary lesion in fifty-seven cases: thirty-five times on the right side; eleven times on the left side; seven times the glands on both sides were equally involved; and four times the oldest lesion was in a gland at the bifurcation of the trachea. Calcareous nodules were present in the bronchial lymph nodes of four children.

In no instance were the bronchial glands alone affected. However, a 3 year old child had two cheesy tubercles in one bronchial lymph node at the root of the left lung, and the pia mater was the only other structure involved in the tuberculous process. In this hospital it is only in older children that tuberculous meningitis has been encountered without generalized tuberculosis.

Lesions apparently of equal age in both the lungs and the bronchial nodes were seen in thirty-six cases, three times with calcareous degeneration in both gland and lung.

TUBERCULOSIS PRIMARY IN THE DIGESTIVE TRACT

The digestive tract was the seat of the primary lesion in nine cases which came to necropsy. The mesenteric glands contained the oldest tuberculous focus in the body seven times. In one infant the mesenteric glands and the intestines showed lesions of apparently equal age, and in another the cervical glands presented the oldest lesion. Only three of these nine children showed no evidence. of tuberculosis in the lungs or bronchial glands. In two the lungs were free, but tubercles were found in a bronchial gland. There were four children whose lungs contained recent miliary tubercles, while their bronchial nodes were free. Evidently the route of infection was through the blood stream in these cases. In only five of the 184 necropsies were the lungs not involved, and in only seven were the bronchial glands not the seat of tuberculous lesions.

Lesions of about equal age were found in the respiratory and in the digestive tract in seven instances, three times with calcareous areas present in both the mesenteric and bronchial lymph nodes. Such cases suggest that at the time of exposure the tubercle bacilli were both swallowed and aspirated.

TUBERCULOUS MENINGITIS

Tuberculous meningitis was present in 53 per cent. of the children in this series; none recovered. The patients were from 9 weeks to 5 years of age; 39 per cent. were under 1 year and 76 per cent. under 2 years of age; that is, 40 per cent. of the infants in our series who contracted tuberculosis died of meningitis before they were 2 years old. Necropsies were performed in 123 cases of tuberculous meningitis. In 116, the primary lesion was found in the respiratory tract, and the children were evidently infected by aspirating the tubercle bacilli. Three children who died of meningitis had the primary lesion in the intestines and mesenteric nodes, and they must have been infected by ingestion of the bacilli. One of these three cases occurred in a female infant, 9 months old; the cervical glands became infected during the fourth month of life and were incised one month later. She developed tuberculous meningitis in the ninth month and the tubercle bacilli in the spinal fluid were proven to be of the bovine type, which is a much rarer cause of meningitis than is the human type of tubercle bacilli. The infant had been nursed

during the first two months of life and then fed on raw cow's milk. This seems to be clearly a case of food infection.

There were four cases of tuberculous meningitis in which the lesions seemed equally old in both the respiratory and the digestive tracts. In these cases the bacilli were swallowed and aspirated at the time of exposure.

That tuberculous meningitis is usually associated with a generalized tuberculosis is shown by the fact that the average number of organs containing tuberculous lesions was nine in babies under 6 months old, and from seven to eight in infants aged from 6 months to 2 years. An exception to this rule has been cited.

The youngest infant with tuberculous meningitis in this series was only 9 weeks old. The mother had active pulmonary tuberculosis, consequently the baby was nursed for only three days and was then fed raw cow's milk. A cough developed when the patient was 6 weeks old, and symptoms of meningitis 3 weeks later. Tuberculids appeared on the skin of the chest and abdomen. At necropsy a very generalized tuberculosis was found, involving the skin, pia mater, pleura, lungs, bronchial and mediastinal lymph nodes, pericardium, thymus gland, liver, spleen and kidneys. A cavity in the right upper lobe seemed to be the oldest lesion. This infant presented a very typical picture of aspiration tuberculosis contracted from his mother, becoming generalized within two months and terminating with meningitis at the age of 71 days.

TUBERCULOUS PERITONITIS

There were twenty-eight cases of tuberculous peritonitis in this series. Only five came to necropsy. Laparotomy was done on three of the children and tuberculous masses were reported in the abdomen of each. The youngest of these twenty-eight children was 5 months old; only four were less than 1 year old; six were 3 and 4 years old; that is, only 36 per cent. of the children in our series who had tuberculous peritonitis were under 1 year old, while 64 per cent. were beyond their second year.

The peritoneum is more often involved in the tuberculous process in older children than in young infants. The youngest infant (aged 5 months) who had tuberculous peritonitis showed, at necropsy, a calcareous area in a mesenteric node as the oldest focus of a tuberculosis which had become generalized and which involved the liver, spleen, stomach and intestines, while the lungs and bronchial glands showed only recent tubercles. In two of the peritonitis patients, aged 13 months and 2½ years, respectively, the lungs were entirely free of any tuberculous lesion and infection was limited to the abdomen.

In one case, a child 3 years old, it was not possible to locate the primary focus, because the lungs contained a large cavity, the bronchial and mesenteric lymph glands were enlarged and cheesy, and the intestinal ulcers were numerous, large and deep.

Tuberculous peritonitis and tuberculous meningitis occurred in a little girl aged 3 years, who gave no history of exposure to tuberculosis. An operation for an abscess of the appendix at the age of 2½ years was followed by an unhealed sinus. A second operation, five months later, showed the presence of tuberculous mesenteric lymph nodes, tubercles on the peritoneum and adhesions between the coils of the intestines. Meningitis developed three weeks later and resulted in death after one week. At necropsy all the mesenteric lymph glands were found to be cheesy and many of them contained calcareous areas, while the bronchial nodes were neither enlarged nor cheesy. Miliary tubercles were present in the lungs, liver and spleen, and old ulcers were found in both the large and small intestines. The mesenteric nodes were the seat of the primary lesion.

THE HEART

The heart is rarely involved in tuberculosis in young children. In cases with very generalized lesions, both in young infants and in children over 2 years of age, recent small gray tubercles are sometimes found on the visceral pericardium, more rarely on the endocardium, especially over a pectinate muscle, or in the myocardium. Tubercles in the heart are rarely more than six in number and usually there are only from one to three. Occasionally, the ascending arch of the aorta may be the seat of tubercles. In our series tubercles were seen in the visceral pericardium in eleven cases, on the endocardial lining five times, and in the heart muscle five times. In two cases small tubercles were present on the surface of the aorta just above the origin of the vessel.

Exudative tuberculous pericarditis is very rare, only one case occurring among the 184 necropsies studied. This condition is of such interest and infrequency that a detailed report seems desirable. A boy, 11 months old, developed pulmonary tuberculosis after an attack of pertussis when 7 months old. At necropsy the pericardial sac measured 7 cm. across the base and 9 cm. from base to apex. The visceral and parietal layers were adherent by means of a cheesy exudate from one to two cm. in thickness, which enveloped the entire heart, completely obliterating the pericardial cavity. The myocardium of the left ventricle was 2 cm. thick, and of the right ventricle 1½ cm. thick. A yellowish cheesy layer in both ventricular walls occupied all but the innermost 3 or 5 mm. of myocardium. There was a

large cheesy cavity in the right lung, while miliary tubercles were present throughout both lungs and in the pia mater, liver, spleen, bronchial and mesenteric glands.

SKIN

Tuberculids of the skin were found in only four of our cases, all young infants, aged 8 weeks, 3 months, 5 months and 13 months, respectively. The three youngest patients died of tuberculous meningitis. All had a very generalized tuberculosis.

SUMMARY

This study emphasizes the following facts:

1. The great frequency of tuberculosis in infancy and early childhood.

2. The suggestive decline of tuberculosis among the young children admitted to the Babies' Hospital during the last six years.

3. The greater incidence of tuberculosis of infants and young children acquired by inspiring tubercle bacilli compared with that acquired by swallowing the bacilli with milk or food.

4. The rapid generalization of tuberculosis in young subjects, the rapidity and degree of generalization being, as a rule, in inverse proportion to the age.

5. The great frequency with which termination by tuberculous meningitis occurs.

6. The absence of any case of healed tuberculosis from this series of 184 necropsies on tuberculous children.

THE FAT CONTENT OF FECES OF YOUNG CALVES [*]

PAUL E. HOWE

PRINCETON, N. J.

New-born calves excrete feces during the first week of life which show distinct variations in the gross appearance. A study was made, therefore, of the amount of fat present in the feces, from birth to the time when the calves were approximately a week old. It is during this time that the calf readjusts its metabolic activities from that of an intra-uterine existence to one in which it subsists by absorption from its gastro-intestinal tract. It was found in general that the fat content of feces increases from birth to approximately the third day, after which it decreases and assumes an approximately normal level. At the time of the high fat content, there is present in the feces a greater proportion of fatty acids in the form of soap, indicating a lack of absorption on the part of the young animal.

METHOD

The method used for the determination of fat was a modification of the method developed by Saxon,[1] which is in itself a development of the method of Meigs, for the determination of fat in feces. It seemed advisable to estimate the quantity of soap present in feces, as well as the total fat and fatty acids present as free fatty acids and soap. To do this we first extracted moist feces with ether and alcohol, according to the Saxon procedure, and then to the residue added hydrochloric acid to liberate the fatty acids from the soaps. The ether layer when removed contains a small amount of alcohol and acid; it was, therefore, collected in a separatory funnel and washed with distilled water until free from chlorids. This precaution is necessary to prevent the formation of ethyl esters of the fatty acids present. Comparative analyses showed this procedure to give, with suitable precautions, the same results as in the Saxon procedure.

After we had commenced our analyses, the modification of the Röse-Gottlieb method by Holt, Courtney and Fales [2] appeared. These investigators applied a somewhat similar procedure to dried feces, by extracting with combined ether and petroleum ether. They derived their value for soaps by subtracting the results obtained by a nonacid

1. Saxon, G. J.: J. Biol. Chem. **27**:99, 1914.

2. Holt, L. E.; Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. **17**:38 (Jan.) 1919.

extraction from that obtained by an acid extraction. When such a procedure is applied to work with fresh feces we do not obtain results comparable with those obtained by a second extraction, i.e., fat is obtained through the second extraction which does not appear in the first extract.

From our experiences with this modified Saxon method for the determination of fat and for the distribution of neutral fat, fatty acids and soap in feces, we have found that the method gives consistent results for total fat. When used for the estimation of fatty acids and for the estimation of soap and free fatty acids as we have modified it, the method gives fairly satisfactory results. In feces of a high fat content, rich in soap, the double extraction tends to give low results for total fat, but the loss appears to be in neutral fat rather than in the fatty acids and soap. We had hoped to develop the double extraction method to such an extent that we could dispense with the acid extraction but found it necessary to continue our determination according to the Saxon procedure as well as our own as a check on the results. For the acid alcohol-ether extraction the method in detail is as follows:

From 5 to 6 grams of thoroughly mixed moist feces are weighed into a 100 c.c. glass stoppered cylinder, as suggested by Saxon. A small amount of water is added, and the cylinder is shaken to obtain a thorough mixture of feces and water. Then from 1 to 2 c.c. of concentrated hydrochloric acid is added and the volume made up to 30 c.c. Twenty cubic centimeters of ether and 20 c.c. of alcohol are added and the contents shaken for five minutes after each addition. After the last shaking the cylinder is allowed to stand until the ether-fat layer separates. The ether is blown off into a separatory funnel, containing a small amount of water. Four portions of ether of 5 c.c. each are added successively, the contents agitated, and the ether layer removed.

A second portion of 20 c.c. is then added and the contents shaken for five minutes. This layer is then removed and four 5 c.c. portions are again added and removed. The ether extract is thoroughly washed with water until free from chlorids, transferred to an Erlenmeyer flask and the ether removed by evaporation on a hot plate. The fat residue is then extracted with petroleum ether, boiling below 60 C., and the extraction filtered through a small fat free filter paper, into a weighed flask. The petroleum ether is removed and the fats dried at approximately 90 C. to constant weight. Fifty cubic centimeters of benzol are added to the weighed fat, heated to boiling, and immediately titrated with tenth normal potassium alcoholate. This procedure gives the total fat and fatty acids, present as free fatty acids or soap.

Double Extraction.—The procedure in this case is practically identical with that just described with the following exceptions:

(a) Extraction without Acidification: In the first original extraction the hydrochloric acid is omitted, and the ether extract is passed through a fat-free filter to retain any particles of soap which may be carried over with the ether.

(b) Acidification and Extraction: The residue remaining from the extraction under (a), plus the filter paper from (a), is acidified with from 1 to 2 c.c. of hydrochloric acid and the extraction repeated as outlined. The results obtained under (a) above represent most of the fat and the free fatty acids. The extraction under (b) contains the residual fat, if any, and the fatty acids present as soaps.

We have found that it is necessary to work with fresh feces because when the feces are kept for any length of time there is a gradual transformation of fat into fatty acid as well as rearrangements in the fatty acid-soap equilibrium. One of the largest possible sources of error, as indicated by Holt, Courtney and Fales, is in mixing the feces to obtain a thoroughly representative sample for analysis.

Moisture was determined by weighing from 5 to 7 gm. of moist feces into a weighed lead cap and drying in a vacuum desiccator over sulphuric acid. The hydrogen ion concentration was determined colorimetrically on a filtered water extract of the moist feces using the indicators and standard solutions of Clark and Lubs. Nitrogen was determined by the Kjeldahl method.

SUBJECTS

The animals studied were born at the Institute and kept in stalls separate from their mothers. They were taken to the dam to suckle twice a day, night and morning, or were fed milk from the dam from a pail.

Three calves did not receive colostrum but were given a mixed whole milk. With the exception of number 456 B, which was a Guernsey, all animals were either grade or purebred Holsteins.

COLLECTION OF FECES

The feces were collected in glass jars at the time of defecation. The collections were not quantitative. Analyses were begun soon after collection.

DATA

Data were obtained from fourteen calves, over periods ranging from four to twenty-four days for each animal. Additional preliminary data on samples of feces obtained from different calves at various ages show results similar to those presented as to the sequence of changes in the same calf.

The data are contained in Tables 1 and 2. The results for fat, fatty acids and soap are expressed as percentages, in terms of the moisture-free substance and the nitrogen as percentage of the moisture and fat free substance.

The data show an increase in the fat content from birth to approximately the third day, after which the fat content decreases to a somewhat lower and fairly uniform value. Associated with a high fat content on the third day is noted an increased percentage of soaps.

The physical character of the feces corresponds somewhat to the variation in fat content, the meconium is usually greenish black in color; it may consist of hard balls, or it may be soft and rich in mucus; quite often the latter type of stool follows the former type. Succeeding the meconium are feces yellow in color and of a more or less pasty consistency, often containing fatty acid crystals. This is the stool most characteristic of approximately the third day. Following this is the fairly soft stool, greenish brown in color, the type of feces which persists unless a digestive disturbance occurs. The separation between the two types of feces was very marked—when the two types appeared in the stool they could, as a rule, be differentiated readily.

The fat-soap mixture remaining after titration of the fatty acid was examined for nonsaponifiable material. From 6.1 gm. of fat, fatty acids and nonsaponifiable matter 0.17 gm. of nonsaponifiable material was obtained, representing approximately 2.8 per cent. of the mixture. This value is undoubtedly high. The nonsaponifiable material was largely cholesterol.

During the time that calves are showing the change in the appearance and composition of feces they are receiving a variable diet. The first milk or colostrum is rich in protein and the colostral bodies but is not, according to published analyses,[3] appreciably richer in fat than milk secreted after lactation has proceeded for some time. The colostral bodies do carry the fat in the form of larger droplets than occur in milk.

It seemed possible that the colostrum itself might be responsible for the character and composition of feces passed during the first three days. Three calves, 487 B, 495 B, 474 B were, therefore, fed the whole mixed milk from cows well along in the period of lactation. In all cases the meconium was passed readily, but subsequent defecation was delayed. Calf 487 B passed meconium on the first day and on the second day a sample consisting largely of meconium with a small amount of yellow pasty feces. A sample was not obtained, nor so far as we could determine was passed, between the second and

3. Eckles, C. H., and Palmer, L. S.: Research Bull. 25, Missouri Agric. Exper. Sta., 1916; König., Chem. Nährungs u. Genussmittel, 1: 1903.

TABLE 1.—Composition of the Feces of Young Calves

(Fat percentage of the dry sample. Nitrogen as percentage of the moisture and fat free sample.)

No.	Age, Days	Solids, per Cent.	Total Fat, per Cent.	Neutral Fat, per Cent.	Fatty Acids as Soap, per Cent.	Free Fatty Acids, per Cent.	N, per Cent.	pH
657	½	38.4	11.0	9.8	0.1	1.1		
	1	36.0	14.4	13.4	0.1	0.9		
	3	27.0	15.1	7.7	0.9	6.4		
	4	29.7	14.8	8.6	0.9	4.4		
	5	24.5	9.6	7.0	0.4	2.2		
336B	½	40.9	20.1	18.8	0.2	1.2	7.0	
	2 a.m.	39.6	10.5	6.6	1.0	2.9	11.9	
	2 p.m.	38.3	11.5	6.2	2.1	3.2	12.3	
	3	27.3	6.2	4.4	0.0	1.7	12.6	
	4	27.5	7.0	4.1	0.0	2.9	11.6	
479B	½	43.7	15.1	13.7	0.5	1.0		
	1	40.7	9.1	2.8	4.1	2.2	12.5	
	3	34.1	26.1	17.9	1.4	6.8	12.3	
	6	29.3	7.4	3.6	0.2	3.5	11.6	
489B	1	35.1	16.3	15.4	0.3	0.5	7.6	
	2	40.4	11.9	6.3	2.0	3.6	9.9	
	4	28.6	10.6	7.1	0.2	3.4	12.0	
	7	31.3	9.3	4.1	0.2	5.1	9.5	
	9	29.6	5.8	3.3	0.2	2.2	9.0	
488B	1	44.9	3.4	1.6	0.2	1.7	13.6	
	2	43.0	4.1	1.5	0.2	2.4	13.7	
	4	35.9	12.3	5.2	0.5	6.6	12.0	
	5	43.6	14.6	9.1	0.6	4.9	9.6	
	12	21.9	13.9	7.6	0.4	5.9	8.1	
	13	28.1	43.7	23.1	4.4	16.2	7.8	
	20	31.3	21.7	2.8	13.8	5.1	8.3	
759	1	26.5	6.6	6.1	0.1	0.4	....	6.6
	2	36.3	24.9	14.0	6.6	4.4	....	6.2
	3	36.7	16.3	7.6	1.8	6.9	....	5.8
	4	37.1	11.2	4.3	0.3	6.6	....	6.2
	6	26.0	17.2	8.5	0.9	7.6	....	6.2
	7	28.4	13.9	4.9	0.2	8.8	....	6.2
756	2	38.7	20.2	12.6	1.2	6.4	....	6.2
	3	33.1	24.5	4.4	14.0	6.0	....	6.1
	4	33.1	7.8	2.4	0.1	5.4	....	5.6
	6	45.5	7.9	4.7	0.9	2.4	....	5.6
	7	43.4	10.3	6.4	2.2	1.8	....	5.7
	9	33.6	8.5	3.3	0.5	4.7	....	5.6
465B	1	39.7	14.5	12.9	0.3	1.3	7.3	6.7
	2½	33.9	24.0	14.5	3.7	5.7	9.0	6.2
	3½	33.9	37.5	21.1	4.7	11.7	9.5	5.7
	4½	21.8	10.6	5.6	0.0	3.9	10.1	5.7
	6½	33.3	10.8	5.0	0.5	5.2	11.6	5.6
478B	1	43.4	16.6	14.0	0.3	2.3	....	6.9
	2	34.2	33.0	17.8	7.2	8.1	13.4	5.9
	3	32.7	26.4	12.7	5.5	8.1	13.1	5.4
	8	24.5	16.4	10.3	0.6	5.5	13.1	5.6
480B	1	41.2	3.2	1.3	0.0	1.9	20.2	6.4
	2	46.1	7.7	3.0	1.3	3.4	11.4	5.8
	3	38.1	20.7	15.3	2.2	3.3	11.8	5.9
	4 a.m.	33.1	15.5	10.2	1.5	3.8	11.2	6.1
	4 p.m.	34.7	12.8	9.4	0.6	2.8	11.9	
	5	42.0	14.1	7.8	0.5	3.8	9.3	
477B	1	23.9	16.6	10.3	1.2	5.1	12.6	5.9
	2	29.8	19.7	13.4	1.7	4.6	10.0	5.6
	2	37.7	9.2	4.0	1.4	3.8	12.8	5.6
	3	40.7	27.0	19.6	0.7	7.2	10.2	5.8
	7	30.3	19.8	10.7	0.2	8.9	10.0	5.2

Calves Which Did Not Receive Colostrum

No.	Age, Days	Solids, per Cent.	Total Fat, per Cent.	Neutral Fat, per Cent.	Fatty Acids as Soap, per Cent.	Free Fatty Acids, per Cent.	N, per Cent.	pH
478B	1	40.5	8.7	7.1	0.6	1.1	8.4	
	5	32.1	15.3	5.9	0.3	9.1	8.7	6.8
	6	26.3	51.4	12.4	21.9	16.8	7.5	5.2
	7	26.5	47.3	7.8	21.1	20.2	7.1	6.2
	8	26.6	42.7	4.4	17.5	20.8	6.4	6.4
	11	29.7	22.3	6.6	9.2	6.4	8.2	6.8
	12	28.2	11.7	6.2	1.0	4.4	10.3	6.8
	15	31.7	8.9	6.7	0.0	2.3	8.3	6.6
495B	1	32.5	8.6	7.9	0.3	0.3	6.9	6.8
	7	31.5	16.4	4.6	3.1	8.7	9.9	5.8
	8-9	33.7	18.0	6.3	4.2	8.8	10.4	6.2
	10	28.4	12.8	4.7	3.9	4.3	10.8	
	13	36.2	11.4	5.7	2.3	3.4	8.9	7.2
474B	1	35.6	16.1	14.8	0.3	0.9	7.7	6.8
	5	28.6	13.1	7.1	0.6	5.5	11.3	5.4
	6	25.8	5.6	2.8	0.8	2.2	9.7	6.2
	7	32.4	6.3	3.1	0.0	3.2	9.0	5.4
	8	22.0	9.1	5.3	0.0	3.8	9.0	5.8

fifth days. On the fifth day three stools, small in amount, were passed of approximately the same consistency. An analysis was obtained, on the third sample, the others being unsatisfactory for analysis. These samples were yellow, pasty in consistency similar to those obtained immediately after the meconium. This type of stool was then followed by daily passages of feces, high in fat content and white in color, apparently an abnormal product. It was not until the eleventh day that the character of the feces returned approximately to normal. The other calves, 495 B and 474 B, likewise showed delay of defecation after the passage of meconium. The second sample passed by calf 495 B was obtained on the fourth day after birth but was dropped in the bedding and could not be analyzed. The greenish brown stool ordinarily passed about the fourth day did not appear until the eighth or ninth day. With calf 474 B the second defecation occurred on the fifth day and greenish brown feces appeared on the seventh day. The chemical composition of the feces of these last two calves, if they be considered in the sequence of defecation rather than the actual date after birth on which they were passed, follows somewhat the sequence of changes characteristic of normal feces. We do not feel, therefore, that the increased fat content and high soap is necessarily related to the colostrum.

TABLE 2.—Average Composition of the Feces of Young Calves
with Relation to Age

Age, Days	Number of Analyses Represented in Average	Solids, per Cent.	Total Fat, per Cent.	Neutral Fat, per Cent.	Fatty Acids as Soap, per Cent.	Free Fatty Acids, per Cent.	N, per Cent.	pH
1	13	37.6	13.8	10.6	1.1	2.1	11.8	6.4
2	10	38.4	14.4	8.2	2.1	4.0	9.1	5.8
3	9	33.7	22.2	12.3	3.5	6.4	11.5	5.7
4	9	31.3	11.4	6.3	0.4	4.4	11.4	5.9
5	3	36.7	12.7	7.9	0.5	3.6	9.4	
6	4	33.5	10.8	5.4	0.6	4.6	11.6	5.8
7	4	33.3	13.3	6.5	0.7	6.1	9.7	5.7

In addition to the data recorded, tests were made on a filtered water extract of the feces for the presence or absence of coagulable protein. In practically all cases we found protein present which was coagulable with heat and a small amount of precipitate in cold with acetic acid.

In certain cases in which the coagulable protein was particularly rich, this protein was extracted and examined as to its character, as follows: Feces were worked up with distilled water, acidified with acetic acid, centrifugalized, the proteien precipitated with ammonium sulphate, dialyzed and reprecipitated at least three times. Other precipitations were made with saturated sodium chlorid. Two globulins were obtained, one having precipitation limits for ammonium sulphate between 2.8 and 3.4 and precipitated by dialysis, and the other having

precipitation limits between 3.4 and 4.4, and not precipitated on dialysis. Both proteins were coagulable with heat. In addition protein was obtained on complete saturation with ammonium sulphate coagulable with heat.

SOAP IN FECES

Feces obtained during the second to the fourth day were found by our analysis to be rich in soaps, had a peculiar glistening appearance, and when a small portion of such material was suspended in water, in which it was insoluble, it gave an effect such as occurs when finely divided metal is suspended in gasoline. It was also noticed in the course of the nonacid extraction that white particles tend to accumulate between the aqueous layer and the ether-fat mixture.

It appeared possible that we might be able to separate this material, which we assumed to be and subsequently found to be soap, from the associated material. Portions of fecal material were, therefore, subjected to the procedure adopted for the extraction of fat and free fatty acids, i. e., to nonacid extraction, except that this material was kept suspended in the ether layer by agitation and siphoned off before it could settle. The material obtained was then thoroughly extracted with ether in a separatory funnel. When suspended in a 50 per cent. alcohol-water mixture, by varying the proportions of alcohol and ether, we were able to remove fecal material of greater specific gravity than the soap which had been carried over in the original separation. As a result we obtained a product which was practically pure white, but which on decomposition was found to carry a small amount of yellow pigment which was transformed in an acid solution to a green pigment, evidently a bile pigment. These crystals were thoroughly washed with ether, dried and again extracted with ether until no more extractable material could be obtained. The following results obtained on analysis showed the soap to be chiefly calcium stearate.

TABLE 3.—ANALYSIS OF STOOL FOR SOAP

Weight of sample	0.5849 gm.
Weight of fatty acids	0.5216 gm.
Cacium present	0.0369 gm.
Magnesium	Trace
Titration of fatty acids with 0.1144 N. potassium alcoholate	16.34 C.c.
Molecular weight from calcium determination	283
Molecular weight from fatty acid titration	279
Molecular weight of stearic acid	284
Iodin value	3.9
Stearic acid (Hehner and Mitchell)	86%

DISCUSSION

The changes in composition during the first week of the life of calves indicate that there is a readjustment in the metabolic activities of the calf during the first three days. The data obtained suggest a

fairly complete digestion of fat, but a partial failure to absorb it. Whether or not the failure to absorb the fatty acid is due to a specific condition of the intestinal mucosa or to physical or chemical conditions which influence the combination of the fatty acids with calcium has not been determined. It seemed possible that colostrum might in some way be related to this increased excretion of fat and the excretion of soaps. The effect of colostrum was to delay the excretion of fecal material. Examination of the data in relation to the sequence of defecation without reference to time, in the two calves which may be considered as normal, indicate a somewhat higher fat content of the feces immediately following the meconium.

That there are metabolic disturbances during the first days of life, or earlier, are indicated in the work of various authors. Theobald Smith (unpublished notes) has noted in some cases, the presence of protein in the urine of new-born calves, which disappears on approximately the third day. Reusin [4] and Schloss and Crawford [5] have noted a high uric acid excretion in new-born infants which reaches its maximum on approximately the third day. Kingsbury and Sedgwick [6] have noted a similar phenomenon for the blood of new-born infants. Scours occurs in new-born calves ordinarily within the first three days. It seems to us that the increased fat content of the feces of new-born calves on the third day is probably associated with the other readjustments which are taking place in the animal. It is interesting that in a change of diet such as from fasting to a normal diet, metabolic activity is readjusted to the new plane in approximately three days. [7]

CONCLUSIONS

1. Data have been presented showing the presence of a high fat content on approximately the third day in the feces of new-born calves. This high fat content is accompanied by a relatively high percentage of soap.

2. Calves which did not receive colostrum passed the meconium readily but showed a delayed defecation subsequently.

3. From feces of high soap content nearly pure calcium stearate was separated.

4. Reusin, H. Z.: Geburtsh. u. Gynäk. **32**:36, 1895.
5. Schloss, O. M., and Crawford, J. L.: Am. J. Dis. Child. **1**:203 (Feb.) 1911.
6. Kingsbury and Sedgwick: J. Biol. Chem. **31**:261, 1917.
7. Howe, Mattill and Hawk: J. Am. Chem. Soc. **33**:568, 1911.

CHRONIC TUBERCULOUS HILUS PNEUMONIA IN CHILDREN *

DAVID GREENBERG, M.D.

Assistant in Pathology and Admitting Physician, Lebanon Hospital

NEW YORK

No disease has received more attention in the literature than tuberculosis, especially pulmonary tuberculosis, yet the subject is by no means exhausted. There is a type of pulmonary tuberculosis infrequently met with in children which is often overlooked, unless constantly kept in mind.

The most frequent form of tuberculosis in children, aside from tuberculous meningitis and miliary tuberculosis, is tuberculous pneumonia, either of the lobar pneumonic or bronchopneumonic type. Chronic tuberculosis as met with in adults is almost unknown in infants and children under 2 years of age. With the aid of the roentgen ray more cases of the chronic and subacute forms are being discovered. (Reuben,[1] Dunn,[2] Eisler,[3] and Wesler and Bass,[4] speak of such cases.)

The type of tuberculosis to which I wish to call attention may be defined as a diffuse or parenchymatous process involving that portion of the lung immediately adjacent to the hilus. It is characterized by a gradual onset, comparatively mild constitutional symptoms, fairly definite physical signs (except early), and, as a rule, ends in recovery.

The mode of entry, as in most other forms of pulmonary tuberculosis, is probably through the respiratory tract, according to the views of Hamburger,[5] Ghon[6] and Dunn[2] in this country. This point is by no means definitely settled.

The pathology is not definitely known. There are no necropsy reports and we only know the roentgen-ray and clinical findings, as determined by physical examination. Early roentgenologic studies reveal considerable enlargement of the tracheobronchial glands. This

1. Reuben, M. S.: Fever, Initial Sign in Tuberculosis of Children, Arch. Pediat. **33**:171, 1916.

2. Dunn, C. H.: Tuberculosis in Infancy, Am. J. Dis. Child. **11**:85 (Feb.) 1916.

3. Eisler, F.: Die Interlobare Pleuritische Schwarte der Kindischen Lunge im Roentgenbilde, München. med. Wchnschr. No. 35, 1899 (Aug.) 1912.

4. Wessler, H., and Bass, M. H.: Recurrent Hilus Infection in Children, Am. J. Dis. Child. **11**:198 (March) 1916.

5. Hamburger, F.: Die Tuberculose des Kindesalters, Leipzig u. Wien., 1912.

6. Ghon, A.: Der Primäre Lungenherd bei der Tuberculose der Kinder, Berlin u. Wien., 1912.

would speak for a direct extension from the glands into adjacent
lung tissue. The process usually assumes a more or less triangular
outline, with the base toward the hilus, according to Wesler and
Bass, who have studied these cases roentgenologically. The apex
has a tendency to follow the interlobar fissure. The lesion is more
common on the right side, and the shadow is irregular both as to
outline and density in different parts of the lung. There is no great
tendency toward cavity formation or calcification. When healing
occurs there may be very little evidence of fibrosis or scar forma-
tion, either as determined by physical signs or the roentgen-ray
examination.

The clinical history is not uniform. The earliest manifestations
are irregular fever (Fig. 1), occurring in a child otherwise well,
and stationary or slight loss in weight. The early fever in tubercu-
lous children was emphasized by Reuben.[1] It may occur at an
early age. One of my patients became ill when 12 months old.
Sluka's[7] statement that chronic tuberculosis of this type does not
occur under two years does not seem to be without exception. The
fever is at first moderate, from 101 to 102 F., and may either be
remittent or intermittent. With the fever there is increase in pulse
rate, fretfulness and considerable sweating. As the disease pro-
gresses, the fever becomes higher, from 103 to 104 F., the pulse
becomes more rapid and there may be some gastro-intestinal dis-
turbances, especially in infants when the fever is high. Profuse
perspiration is an early and frequent accompaniment of the fever and
usually occurs in the early morning hours (Fischberg[8]).

Cough occurs sooner or later. It may be very slight in the
early stages and is often overlooked, but it becomes more manifest
later. Dyspnea may be mentioned as an early symptom, especially
on exertion, as when the child is examined. The child then breathes
as if there were some expiratory obstruction, reminding one of the
neighing of a horse and somewhat resembling asthmatic breathing.

The physical signs, too, are variable. Early they may be absent
or so slight as not to be detected. The first sign in one of my cases
was diminished breathing. Frazer[9] gives dulness as the earliest sign
of tuberculosis in children. As the disease progresses the dulness
and diminished breathing become more marked and distant bronchial
breathing also may appear. Râles are often present, especially along

7. Sluka, E.: Die Hilus Tuberculose des Kindes im Roentgenbilde, Wien.
klin. Wchnschr., (Feb.) 1912, p. 259; ibid., (Feb.) 1913, p. 254.

8. Fishberg, M.: Pulmonary Tuberculosis, Ed. 2, Philadelphia, Lea &
Febiger, 1919; Diagnosis of Pulmonary Tuberculosis in Children of School
Age, Med. Rec. **92**:406 (Sept. 18) 1917.

9. Frazier, K.: Early Tuberculosis in Children, Brit. J. Tuberc. **9**:1, 1915.
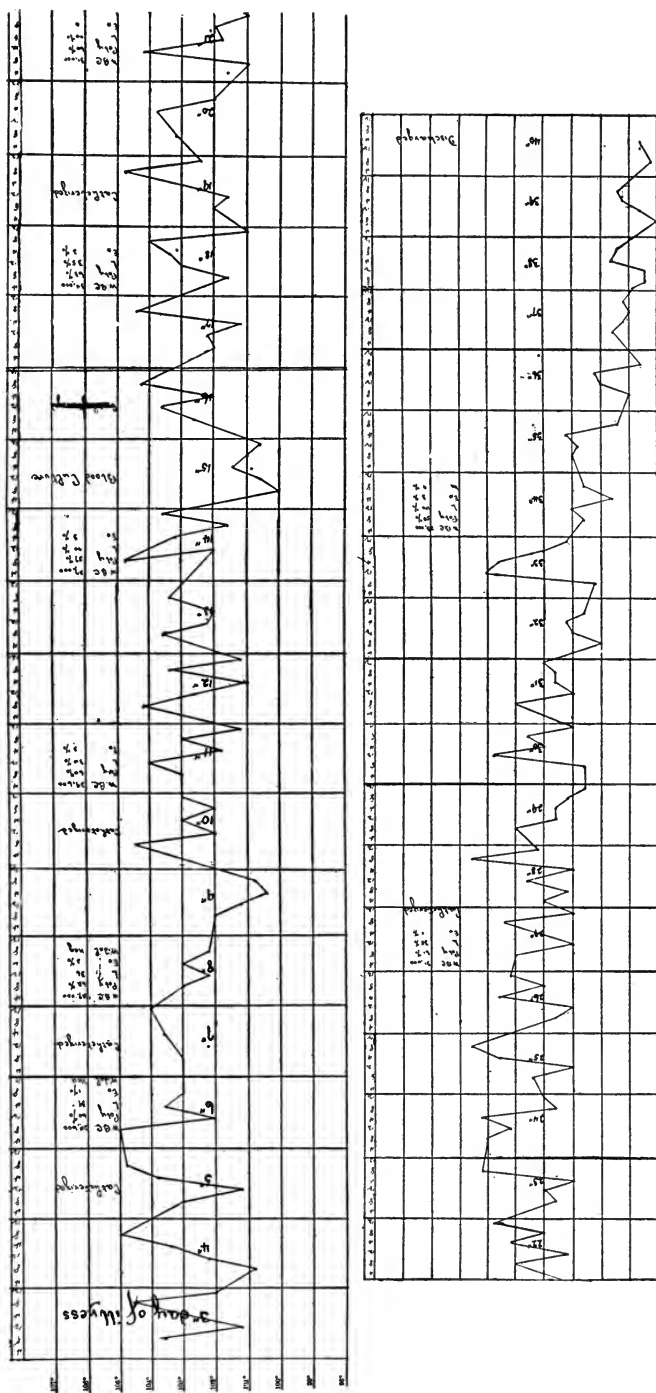
CHART 1.—Case 1

Fig. 1.—Temperature record in Case 1 during the first thirty days of illness.

the margins of the process, when it is extending. Late there usually are râles over the entire lesion. These signs may extend and become so definite that the presence of fluid or large pulmonary abscess is diagnosed. Increased respiration, limitation of expansion, increased fremitus and retraction may also occur. The liver and spleen were enlarged in one of my cases and there were palpable glands in the supraclavicular fossa.

The course of the disease is toward recovery. It may, however, last for many months or even years.

There may be a leukocytosis. There are not many reports as to the blood picture in the literature. My own observations seem to indicate that a high white blood count is not incompatible with tuberculosis in infants and children. In one of the cases here reported the white blood count was persistently high, ranging from 24,000 to 34,000 per c.mm., with a polymorphonuclear percentage of from 64 to 71. The urine may show a trace of albumin, even in the absence of other evidence of renal involvement. There is no particular tendency toward anemia. The sputum is scanty and it requires persistent effort and painstaking examination in order to demonstrate tubercle bacilli. In one of my cases it was only after the twentieth examination that I was able to demonstrate tubercle bacilli in the sputum. Injection of the sputum into a guinea-pig may demonstrate tubercle bacilli earlier. The roentgen-ray findings were discussed under pathology.

The diagnosis may be made more often if Hamberger's [5] dictum, "think of tuberculosis when no other diagnosis can be made," and the possibility of this kind of tuberculosis, is kept in mind. Given a child with prolonged irregular fever, even without definite lung signs, tuberculosis should be suspected. When in addition to the fever there is dulness and diminished breathing and only an occasional cough, or dyspnea, tuberculosis must be considered until ruled out. The following diagnostic points are relied on: (1) Von Pirquet; (2) sputum examination; (3) roentgen-ray examination; (4) lung puncture, and (5) enlarged supraclavicular glands.

Von Pirquet: The von Pirquet is of more value than it is generally believed to be. Frazer [10] regards it as of distinct value even up to the tenth year. Veeder and Johnson [11] are of the same opinion. It certainly is of great value up to 2 years of age.

Sputum Examination: The presence of tubercle bacilli found either by direct examination or on guinea-pig inoculation, makes the diagnosis.

10. Frazer, T.: The Significance of the von Pirquet, Med. Rec. **87**:57, 1915.
11. Veeder, B. S., and Johnson, M. R.: The Frequency of Infection with the Tubercle Bacillus in Childhood, Am. J. Dis. Child. **9**:478 (June) 1915.

Roentgen-Ray Examination: A characteristic triangular shadow is to be considered presumptive evidence of this form of tuberculosis.

Lung Puncture: The method of puncture recommended is to use a fairly large needle with a little sterile water in the needle or syringe. Introduce the needle in several directions and aspirate. When it is withdrawn empty the contents of the needle into a sterile test tube. The material thus withdrawn is divided into several portions and examined for the presence of tubercle bacilli by direct spread, for giant cells, and some of it is injected into a guinea-pig.

Enlarged Supraclavicular Glands: Enlarged glands just above the clavicle on the side of the lesion is another point strongly suggestive of active tuberculosis.

This type of tuberculosis has to be differentiated from the following diseases: unresolved pneumonia, either with or without bronchiectasis, pulmonary abscess and encysted empyema, tracheobronchial adenitis, foreign body in the lung, actinomycosis, neoplasm of the lung and streptothrix infections.

The prognosis of tuberculosis (pulmonary) in children is rather serious. The younger the patient the graver the outlook, yet in this type of tuberculosis, as in tracheobronchial adenitis, the prognosis is favorable. The patients whose cases I am reporting recovered, at least clinically. The patients of Wesler and Bass,[4] which evidently belong to the group, also recovered. Increase in weight, steady diminution in temperature and decrease or entire disappearance of cough, are among the early favorable signs.

The treatment is not different from that generally advised for other forms of pulmonary tuberculosis. It consists in the dietetic and hygienic régime. A change of climate is advisable if circumstances allow it. The child should reside in the country, preferably at a considerable altitude, for a year or more. The open air and heliotherapy recommended by Freeman[12] for other pulmonary conditions is of great value here also. Sleeping outdoors is comparatively simple for a child if an intelligent mother or nurse is in attendance. The diet should be liberal, but great care must be exercised against overfeeding, especially in the younger patients.

REPORT OF CASES

CASE 1.—(This case was published incompletely in a previous communication.[13]) B. B., female, 1 year old.

Family History.—Negative.

Previous History.—Normal birth, breast-fed up to 7 months, mixed feeding up to the tenth month, weaned at 10 months. Put on formula of top milk. Did well up to present illness.

12. Freeman, R. G.: Fresh Air in Pediatric Practice, Am. J. Dis. Child. **12**:590 (Dec.) 1916.

13. Med. Rec. **97**:736, 1920.

Fig. 2.—Case 1. Triangular hilus infiltration with the apex extending along the interlobar fissure.
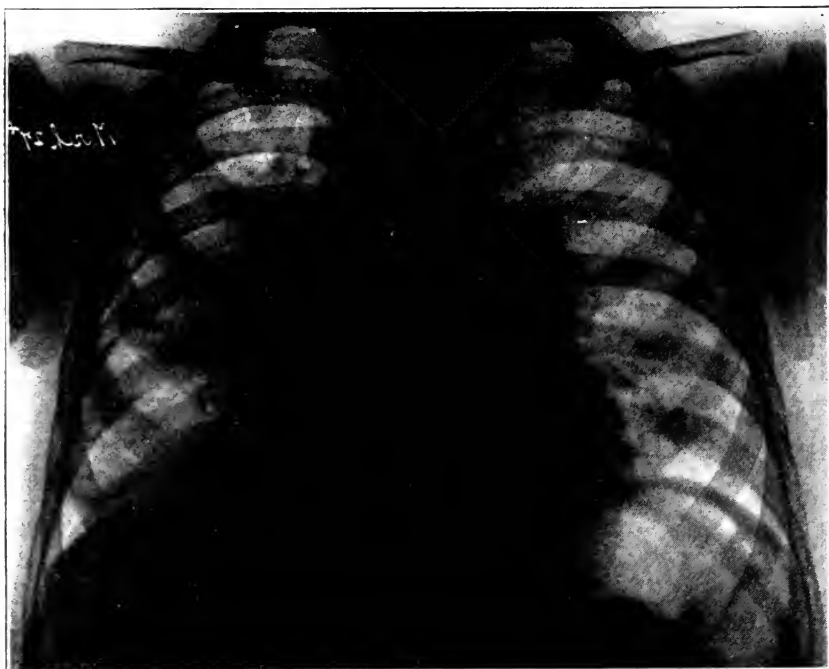

Fig. 3.—Case 1. The hilus infiltration is less definitely outlined than in Figure 2.

Present Illness.—Became ill with a temperature of 102 F., vomited twice at onset; was treated for influenza for two days before I saw her.

Physical Examination.—On examination, I found a fairly well nourished child, not perceptibly prostrated; temperature 103.5 F., fairly rapid pulse; respiration about 30 and acid breath. The skin and glands were negative, as were the mucous membranes; no catarrhal symptoms. The rest of the examination was negative, except for a palpable liver and spleen.

Diagnosis.—A diagnosis of acidosis was made, and the child was treated accordingly. The irregular fever, however, continued for over a month, uninfluenced by treatment. The course of the fever is interesting. It would remit several times during the twenty-four hours and was often highest in the morning and after sleep. The child perspired rather freely. During this period the child never vomited again, had no diarrhea, took its food fairly well and slept normally. The child was examined by several consultants and nothing characteristic was found. I had noticed slight dyspnea several times, but paid no particular attention to it.

Laboratory Examinations.—Several blood examinations showed a high leukocytosis, from 24,300 to 31,000, with from 60 to 65 per cent. polymorphonuclears. Blood and urine cultures were negative.

Date	Leukocytes,	Polymorpho-nuclears, per Cent.	Lympho-cytes, per Cent.	Eosino-phils, per Cent.	Mononuclears and Transitionals, per Cent.
Nov. 26	24,600	60	39	1	—
Dec. 4	27,000	57	40	3	—
Dec. 8	34,000	63	35	2	—
Dec. 17	31,000	61	38	1	—
Dec. 24	23,000	54	40	2	4
Feb. 4	26,000	64	30	—	6
Mar. 15	39,600	71	29	—	—
April 4	28,000	69	28	1	2
Jan. 29	29,000	67	33	—	—

Clinical Course.—At the end of about thirty-two days the temperature came down by lysis and remained about normal for several weeks, when it mounted again. About this time the dyspnea became more marked, especially on exertion. This dyspnea was expiratory and was suggestive of pressure behind the pharynx. A search for retropharyngeal suppuration was negative. Diminished breathing over the right lobe posteriorly and slight impairment of resonance was also noticed at the same time.

In the meantime pus was found in the urine and our attention was called to the possibility of latent pyelitis being responsible for the entire clinical picture. Clearing up of the pyuria was not associated with disappearance of the other symptoms, but the diminished breathing and resonance became somewhat more pronounced and the child was then fluoroscoped and radiographed. The roentgenograms showed a triangular area (Figs. 2, 3, 4, 5, 6 and 7), the true nature of which was not then detected.

The diagnosis (roentgenographic) at that time was multiple abscesses or encysted empyema and operation was advised. Chest puncture, however, failed to locate the pus, and the material obtained was injected into a guinea-pig. A von Pirquet test was made about this time and proved strongly positive. Before the guinea-pig could be killed, tubercle bacilli were found in the sputum after more than twenty examinations were made. Two weeks later the guinea-pig showed tuberculosis.

We were reluctant to consider this case tuberculous because of the blood count, which persistently showed a high leukocytosis, and
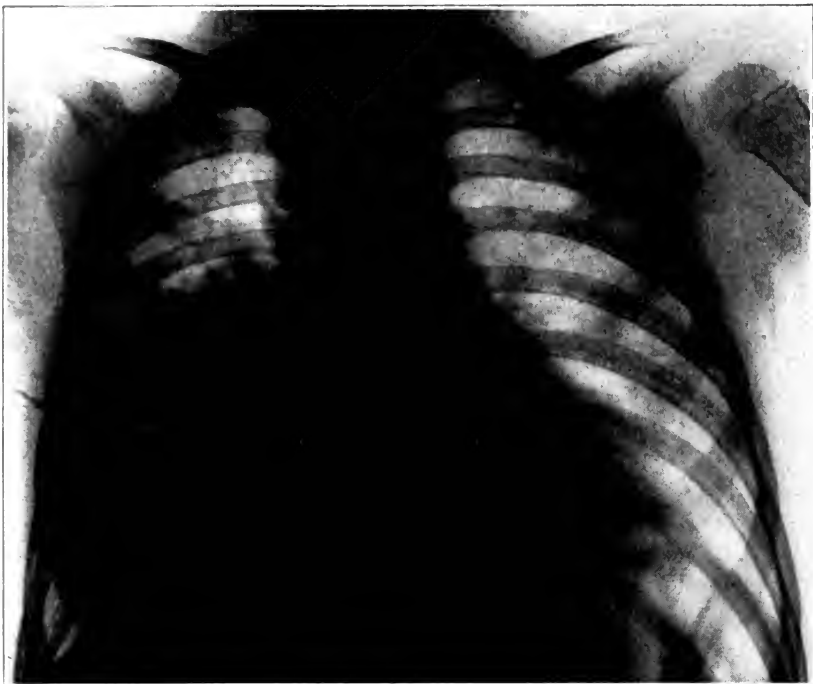
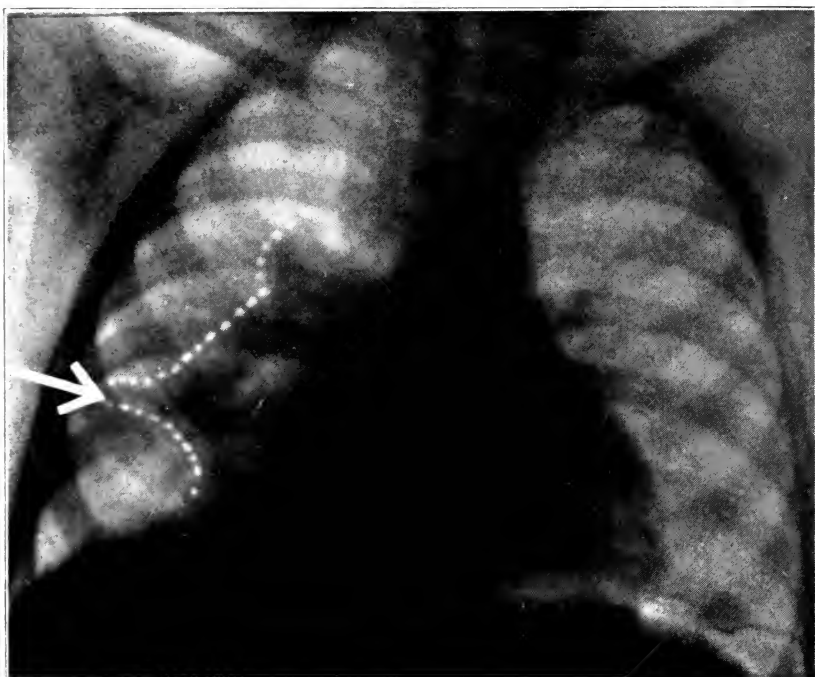Fig. 4.—Case 1. Several weeks later, the process apparently was extending.

Fig. 5.—Case 1. The process is seen extending along the interlobar fissure. The arrow indicates the presence of free air.
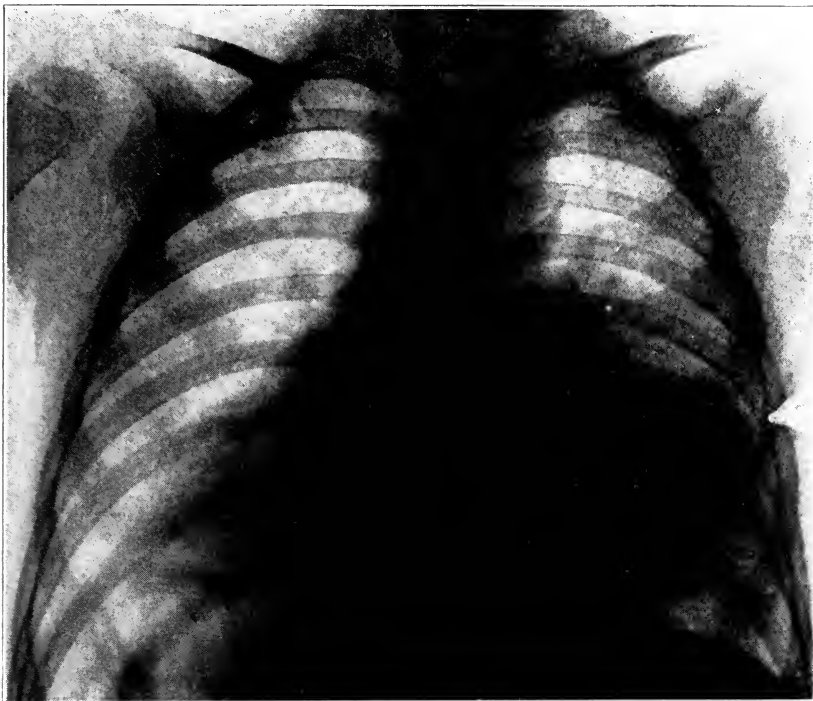
Fig. 6.—Case 1. The process is seen extending along the interlobar fissure.
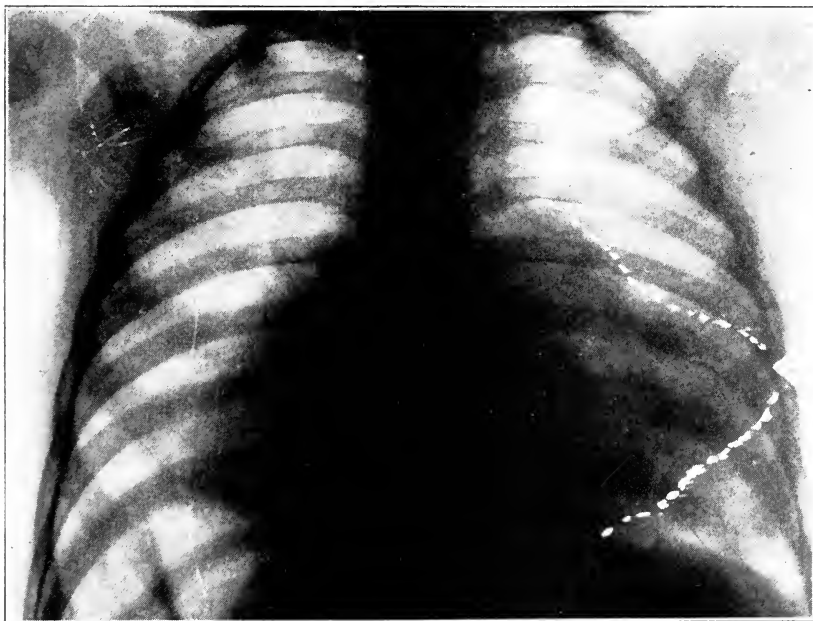

Fig. 7.—Case 1. After a short stay of the patient in the country, the shadow is less dense.

the relative freedom of the upper part of the lung from all evidence of infiltration. The sputum examination and the results of the guinea-pig inoculation definitely established the diagnosis.

After the diagnosis was established, the child was sent to the country and began to improve almost immediately so that now, about a year and a half after the first onset of illness, the child is apparently almost entirely well.

CASE 2.—H. C., male, aged 17 months.

Family History.—One brother died of meningitis (?).

Previous History.—Normal birth, fourth in the family, breast-fed up to 11½ months, no other illnesses. Was told he had enlarged tonsils and adenoids.

Present Illness.—Became ill about June, 1919, with fever, which, according to mother's statement, would come and go. The child was seen by several physicians within the first four weeks of its illness and various diagnoses were made. The family at first did not think that the child's condition was serious, but they became worried after the fever had lasted about a month. While the child had fever almost every day it would still play and would not stay in bed. The mother did not know how high the fever was. When I first saw the patient he had grown perceptibly worse. He had begun to sweat more or less profusely, especially after sleep, and had occasional attacks of hoarseness. No cough was noted previous to this time.

Physical Examination. — Patient was a fairly well nourished child, but slightly prostrated; skin and mucous membranes negative; temperature 103.2 F., pulse 136, respirations 28; head somewhat square-shaped, fontanel open; palpable cervical lymph glands; two very small lymph nodes in right supraclavicular fossa. Chest shows a slight rachitic rosary; moderate dulness over lower lobe posteriorly, except at the very base; relative dulness in right axilla, diminished breathing in axilla, distant bronchovesicular breathing posteriorly, a few fine crepitant râles in the axilla and posteriorly just below the angle of the scapula. The rest of the examination is negative.

Laboratory Examination.—The urine was negative. The sputum, which was obtained by tickling the larynx and catching the coughed-up material on sterile gauze, was negative on three occasions. The blood count was 16,400 leukocytes, with 65 per cent. polymorphonuclears. A chest puncture yielded no fluid and some of the material withdrawn, which consisted of blood stained detritus, was injected into a guinea-pig. Some of this material showed tubercle bacilli by direct spread examination.

The roentgenograms were almost identical with those of Case 1, i. e., the lesion was on the right side, triangular in outline, irregular in density, with a tendency to follow interlobar fissure (Figs. 8, 9, 10 and 11). The roentgenologist made a diagnosis of interstitial pneumonia, probably caused by a foreign body and advised a bronchoscopic examination which, of course, was not done. Subsequently, tubercle bacilli were also found in the sputum. The leukocyte count remained between 16,000 and 21,000.

SUMMARY

1. Extensive tuberculous lesions about the hilus may occur in infants and young children which pursue a rather chronic course.

2. Recovery probably takes place in the majority of these cases even in children under 2 years of age.
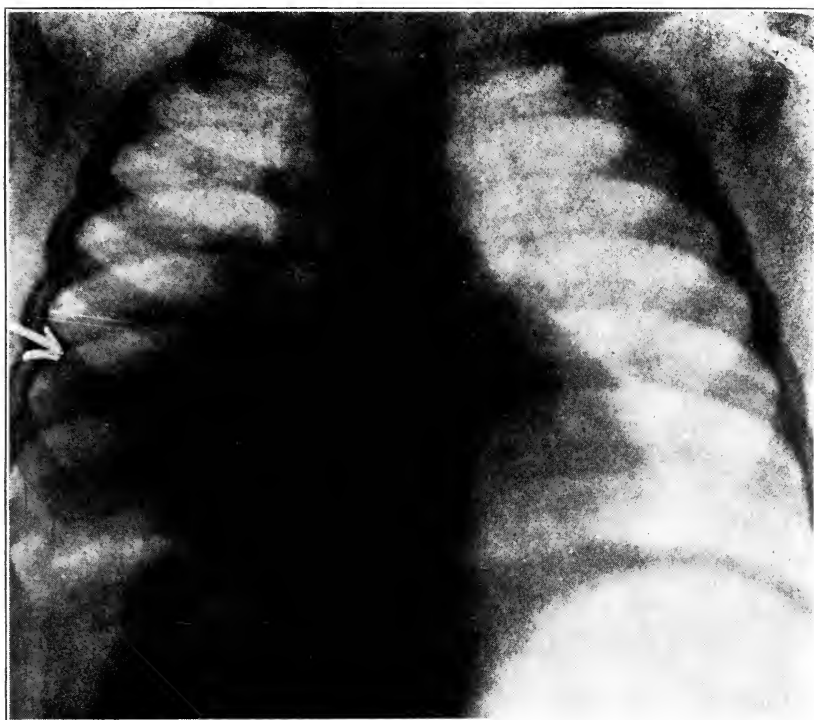
Figure 8

Figure 9

Figs. 8 and 9.—Case 2. Characteristic triangular outline, base toward hilus.

Figure 10
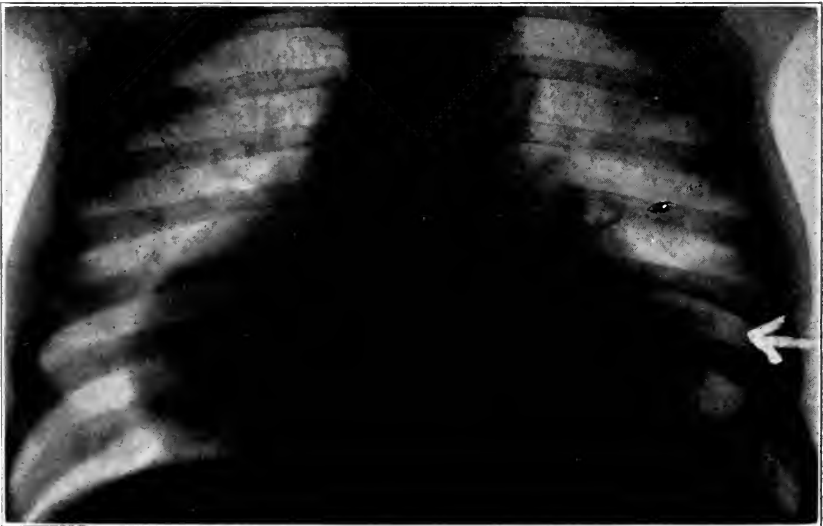
Figure 11

Figs. 10 and 11.—More extensive involvement with irregular density at a time when there began to be clinical improvement.

3. The onset in this type of pulmonary tuberculosis is more or less gradual and there may be no lung signs until after the disease has lasted for some time.

4. Irregular fever, sweating, expiratory obstruction, diminished breathing, with impaired resonance, a positive von Pirquet and a characteristic roentgen-ray picture, are among the earlier manifestations.

5. Enlargement of the supraclavicular lymph nodes, positive results from guinea-pig inoculation of material from lung puncture or of sputum, and the presence of tubercle bacilli in the sputum may be found later in the course of the disease.

6. Given an infant or child with prolonged irregular fever and sweating, showing a positive von Pirquet, this form of tuberculosis should be suspected and its further early manifestations sought for.

COMPLEMENT FIXATION FOR TUBERCULOSIS IN CHILDREN *

J. V. COOKE, M.D.

ST. LOUIS

The complement fixation test in tuberculosis has become so well known through a number of recent articles on the subject, and the literature has so often been reviewed that a detailed discussion of previous work is unnecessary. All workers have not been able to secure good results with the test and there has been some lack of conformity between the results of the fixation tests and the clinical diagnoses. It may be mentioned, however, that although different preparations of antigen have been used those investigators whose interest in the reaction has led to a considerable experience in performing the tests have obtained the best and most consistent results. The skepticism that exists in some localities regarding the value of the reaction depends to a certain extent on a lack of understanding of the difficulties in securing a close agreement between the fixation tests and the clinical examination.

Probably several factors have contributed to the inability of all workers with the test to obtain uniform results. One of these is the lack of a uniform technic in performing the test. All tubercle antigens are not equally potent in the reaction, and even two antigens made in the same manner may vary considerably. In addition, there is a very marked difference in the concentration of the fixing antibodies in the blood of different individuals so that while one patient's serum may give a positive fixation in 0.002 c.c., another will give fixation with 0.2 c.c. and not with a less amount, and in a third the concentration of fixing antibodies is so slight that even 0.2 c.c.—the largest amount used in routine tests—contains too little to give a positive result.

The presence of complement fixing antibodies in the blood must depend on the existence in the body of some pathologically active focus of tuberculosis, since the absorption of antigen from such a focus is necessary for the formation of such an antibody. If this lesion is large enough and if there is a considerable absorption from it, there may be definite clinical signs and symptoms. On the other hand, it takes only a slight acquaintance with the necropsy room to realize how frequently small active tuberculous foci, or even rather

---

severe infection may be found without having caused clinical manifestations during life. In such individuals, the necessary mechanism existed for the production of complement fixing antibodies in the circulating blood, even though the patients were considered clinically free from the disease. There is, therefore, some difficulty in harmonizing the results of a series of fixation tests with clinical findings, on account of the not infrequent absence of sufficient clinical evidence to arrive at an exact diagnosis.

The attempt to secure an exact agreement between the results of the complement fixation test and patients with clinical signs of tuberculosis, even with a standardized method, would seem foredoomed to failure for two reasons. First, on account of the lack of sufficient fixing bodies in the blood of certain patients with undoubted active tuberculosis and second, because of the impossibility of recognition by present diagnostic methods of small pathologically active tuberculous foci in some individuals without clinical evidence of the disease. That certain workers, after a considerable experience, have been able to secure an agreement between the test and the clinical diagnosis in from 75 to 90 per cent. of cases seems rather to indicate that under proper conditions the test may be of considerable aid in diagnosis. If others have obtained somewhat less encouraging results, the explanation may lie in one of the factors mentioned above.

Although a considerable number of investigators have reported the results of the complement fixation test in tuberculosis, very few have been interested in making group studies in children. These have included a relatively small number of cases and have given almost negative results. Bauer [1] (1909) examined twenty-one cases of tuberculosis including fifteen infants under 2 years and six children from 8 to 10 years old, with forty nontuberculous children having syphilis, pneumonia, etc. All these gave negative reactions with tuberculin antigen. Certain of the patients were treated with injections of tuberculin, and in all cases so treated, the reaction became positive. Fua and Koch [2] also using tuberculin as antigen tested two series of cases of tuberculous children. The first group of twenty-seven patients, ranging in age from 5 months to 13½ years, untreated by tuberculin, all gave negative results except six, which gave a very weak fixation, but not strong enough to be considered positive by the authors. In the second series, fourteen of forty-one children, aged from 4½ months to 14 years, who had had from two to four doses of tuberculin,

1. Bauer: Komplementablenkung bei tuberculösen Kindern, Verhandl. d. Gesellsch. f. Kinderh. **25**:106, 1909.
2. Fua, R., and Koch, H.: Zur Kenntnis der mit Tuberkulin komplementbindenden Stoffe im Serum tuberculöser Kinder. Beitr. z. klin. d. Tuberk. **14**:79, 1909.

gave positive reactions. Heiman,[3] using Miller's antigen of whole tubercle bacilli in salt solution and Petroff's glycerin-potato-broth filtrate antigen, tested fifty children aged from 6 months to 12 years. Seventeen with various forms of tuberculosis gave two positive reactions, five probably tuberculous cases were all negative, and twenty-eight nontuberculous infants and children gave three positive reactions.

The present paper gives the results of the examination of a large number of serums from infants and children by the complement fixation test using an antigen made from human tubercle bacilli. The patients were from the Pediatric Clinic of the Washington University and from the wards of the St. Louis Children's Hospital. The test was made in general as a routine procedure during a period of two years, although for various reasons many children seen during that period escaped the examination. There was no selection of cases but probably more effort was made to include all children with tuberculosis or suspected tuberculosis. It is only by the use of the test in a large number of unselected cases, together with a careful examination of the material, that any conclusions regarding its value may be made. In this series, a large percentage of the cases were subjected to a rather close examination for evidence of tuberculous infection. A certain proportion of clinic cases, as, for example, healthy infants whose feeding was being supervised, children without history of association with tuberculosis who came for relatively trivial complaints or for health certificates, were given only a general physical examination and no skin tests were done. In some cases, children failed to return for the reading of the tuberculin reactions. On the other hand, many children with only suspicious clinical findings were sent for flat or stereoscopic chest plates, had one or more von Pirquet or intradermal tuberculin tests done, and daily temperature observations were made by the mother. Occasionally, they were admitted to the hospital for more careful study. In every case a clinical diagnosis was made without reference to the result of the fixation test. In all 1,855 fixation tests were done on 1,556 children, and it is believed that the series studied is sufficiently large to justify conclusions from the results obtained.

METHODS

The antigen employed consisted of a dried, powdered alcoholic precipitate of human tubercle bacilli grown on Dorset's egg medium, prepared as described previously,[4] and used in a salt solution emulsion of one mg. of the powder to one c.c. The antigenic dose was

3. Heiman, H.: The Complement Fixation Test for Tuberculosis in Infancy and Childhood, Arch. Pediat. **36**:32 (Jan.) 1919.

4. Cooke, J. V.: Complement Fixation with Acid Fast Bacteria, J. Infect. Dis. **25**:452 (Dec.) 1919.

0.1 c.c.   Antigens made from different strains of tubercle bacilli vary considerably in their antigenic and anticomplementary properties and it is sometimes necessary to examine antigens made from several different cultures before securing a satisfactory wide range preparation.   In my experience strains that have been cultured for some time are better than freshly isolated ones, but this may not be constant. Two antigens were used in a large number of tests and but little difference was noted.

The hemolytic system used in the tests was 0.5 c.c. of a 1 per cent. sheep cell suspension, sensitized with two units of rabbit antisheep serum of high titer, and two units of complement (1 c.c. of 1 : 100 dilution of guinea-pig serum).

The patient's serum was inactivated and used in amounts of 0.2, 0.1 and 0.05 c.c.   Two additional tubes of 0.2 c.c. each were tested with simple alcoholic and cholesterolized Wassermann antigens and a control of 0.2 c.c. of serum without antigen was always included. The technic of the ·tests has been previously described [4] in some detail and will only be summarized here.   The tubes with serum, antigen and complement were made up to 1.8 c.c. with salt solution, incubated one hour in the water bath at 37 C., the cells (0.5 c.c.) sensitized with two units (0.2 c.c.) of hemolysin added, and reincubated 30 minutes longer.   Readings were made after standing over night in the ice box.   Only complete inhibition with 0.2 c.c. of serum or less was considered positive.

TABLE 1.—AGE, SKIN TUBERCULIN REACTIONS, AND COMPLEMENT FIXATION
RESULTS IN ALL CHILDREN STUDIED

Age in Years	Skin Tuberculin Test Negative		Skin Tuberculin Test Not Done		Skin Tuberculin Test Positive	
	Total Number	Fixation Positive	Total Number	Fixation Positive	Total Number	Fixation Positive
0- 1	48	1	61	2	11	0
1- 2	50	1	26	0	20	8
2- 4	73	4	60	4	44	17
4- 6	84	5	63	1	48	21
6- 9	160	17	124	12	113	53
9-12	120	13	105	14	102	50
12-15	95	7	82	16	66	31
Total	630	48 7.6%	522	49 9.6%	404	180 44.4%

In order to illustrate the ages of the children examined and the relation of the tuberculin skin test to the fixation reaction, the entire series is tabulated in Table 1.   It will be seen that a skin test was done in about two-thirds of the cases.   Most of these tests were made by the von Pirquet method, but in a considerable number an intracutaneous injection of 0.1 mg. of old tuberculin was done.   Not infrequently the intradermal test was positive after a von Pirquet

test had been negative in the same child. This observation has been made by others and is probably due to the greater certainty of a successful tuberculin inoculation by the intradermal method. In this series the intradermal test has proved much more reliable than the von Pirquet, although in many cases only the latter was done. Somewhat less than half the children with positive skin tests gave positive fixations, while of those with negative skin tests 7.6 per cent. gave positive fixations. The latter group, however, included cases of proved tuberculosis with negative skin reactions and other nonspecific reactions to be mentioned later, so that this figure is somewhat misleading. Approximately 100 children in each year from the first to the fifteenth were examined so that the distribution of the tests is fairly uniform so far as age is concerned.

TABLE 2.—Results of Complement Fixation Reactions in Children
with Tuberculosis

Age, Years	Manifest Tuberculosis			Masked Tuberculosis			Suspected Tuberculosis		Healed Tuberculosis	
	Number Tested	Fixation Positive	Per Cent. Positive	Number Tested	Fixation Positive	Per Cent. Positive	Number Tested	Fixation Positive	Number Tested	Fixation Positive
0– 1	12	0	0	—	—	—	1	0	—	—
1– 2	16	7	44	5	2	40	1	0	—	—
2– 4	26	10	38	10	5	50	3	2	—	—
4– 6	16	9	56	19	12	63	1	0	2	0
6– 9	18	15	83	45	33	73	4	2	8	0
9–12	17	14	82	31	23	74	7	5	6	2
12–15	11	9	82	21	20	95	7	4	4	0
Total	116	64	55	131	95	73	24	13	20	2
4–15	62	47	76	116	88	76				

In Table 2 the results of the fixation tests in children with tuberculosis are summarized. By a careful clinical study of each case, these children have been separated into four groups called manifest, masked, suspected and healed tuberculosis, respectively.

The first group of children with manifest tuberculosis includes the cases in which there was no doubt concerning the diagnosis of an active tuberculous process at the time of examination. In addition to a typical clinical picture, the diagnosis was confirmed in each instance by necropsy, demonstration of the organisms or, especially in the bone cases, convincing and characteristic roentgenograms. There were sixty-six children with generalized tuberculosis, meningitis or pulmonary involvement, and fifty with lymph node, bone or joint tuberculosis. Because of the close agreement in the proportion of positive fixations found in these two groups of children they were tabulated together. In infants under 1 year of age a positive skin tuberculin reaction alone was considered sufficient proof of an active lesion. The results in the group of manifest tuberculosis cases show

a very definite relation to the age.   During the first year no positive fixation reactions occurred, while from the second to the fourth years about 40 per cent. of the children reacted positively to the test.   From the fourth to the sixth year this percentage increased to 56 and above six years over 80 per cent. showed positive reactions.   The small proportion of positive results in the early years of life makes the total percentage of positive reactions somewhat low (55 per cent.), although if the group from four to fifteen years only is considered, the percentage of positive cases is increased to 76.   The substances in the blood which give the complement fixation reaction appear distinct from those antibodies which cause the skin tuberculin reaction. This is shown by the fact that of the eight cases of manifest tuberculosis which gave negative skin tests four gave positive fixation reactions and of the four giving negative reactions, two patients were under 2 years of age and two were 4 years old.   It has been mentioned that children of these ages gave positive fixations in less than half the instances.   These were children with miliary tuberculosis or tuberculous meningitis and in these severe infections such a suppression of the skin reaction is not unusual.

The cases of masked tuberculosis were of particular interest.   In the course of the study increasing numbers of positive fixations were noted in children who had no obvious tuberculosis.   On closer examination, however, these children all showed certain of the symptoms that frequently accompany tuberculosis, such as malnutrition, asthenia, slight fever, anemia, loss of weight, etc., with positive tuberculin skin tests.   Accordingly, a special study was made of all children who exhibited one or more of such clinical signs.   Evidence of tuberculosis was sought by repeated careful physical examination and in most cases roentgenography of the chest.   A more detailed report of this group appears elsewhere,[5] and will merely be summarized.   The characteristic clinical picture includes the following: A history of frequent coughs and colds, attacks of unexplained fever often with afternoon elevations, anorexia, loss of weight and asthenia.   There may or may not be known exposure to tuberculosis.   On physical examination there is more or less malnutrition, occasionally anemia, and chest signs referable to enlarged tracheobronchial lymph glands. The von Pirquet or intradermal tuberculin skin test is positive and in certain instances there is phlyctenular disease of the eye or skin tuberculids.   The diagnosis of masked tuberculosis in cases of this group was made from clinical examination alone and did not rest on any one of the above mentioned points but on a review of all the findings.   It is difficult to prove that these children have active tuberculosis but from the studies made it seems very probable that each

5. Cooke, J. V., and Hempelmann, T. C.:   Masked Juvenile Tuberculosis, Am. Rev. Tuberc. **4**:660, 1920.

of them harbors a tuberculous focus that is pathologically active even though this lesion is not large enough to cause the marked clinical signs and symptoms that we find in more easily recognized cases of tuberculosis in childhood. The complement fixation tests on these children support the view that the process is an active one since the number of positive results in children of the different ages parallels closely those found in the manifest tuberculosis group. The same increase in positive reactions is found as the age advances. The higher percentage (73) for the whole group of masked tuberculosis is due to the relatively small number of younger children studied. If only those over 4 years old are considered, the percentage of positive fixations is the same for the manifest tuberculosis group as for those with masked tuberculosis.

The concentration of the fixing substances in the blood varies considerably in different children as it does in adults. Of the 159 cases of manifest and masked tuberculosis that gave positive fixations, twenty-seven did not react with less than 0.2 c.c. of serum, fifty-five had a minimal fixing dose of 0.1 c.c., and seventy-seven gave fixation in amounts of 0.05 c.c. or less. A few of these latter strongly positive serums upon titration gave fixation with 0.004 c.c. This concentration of fixing antibody in the blood has no demonstrable relation to the type or severity of the disease. Such marked differences in antibody concentration as have been shown to occur in the serums studied suggest the most probable explanation for the negative fixation reaction found in a certain number of cases of active tuberculosis. It would be unusual if some cases did not show an antibody content so low that 0.2 c.c. of serum contains too little to be recognized in the test. For several reasons, however, the routine use of larger amounts of serum is impracticable.

In a certain number of instances, the presence of tuberculosis was suspected from certain findings but the examinations were incomplete. These cases could be included neither with the tuberculosis groups nor with those free from tuberculosis so they were classified separately and called "suspected tuberculosis." About half of this small group showed positive fixations.

It was possible to examine only twenty cases of healed tuberculosis. These children had all been observed during an active tuberculosis some years previously. Both pulmonary and bone tuberculosis cases were represented and all had been free from any sign of the disease for from two to six years. Only two of this group gave positive complement fixation tests. Since these children were all over 4 years of age, the results give additional evidence of the association of active tuberculosis with a positive fixation reaction.

Before taking up the control group of children without clinical tuberculosis, two conditions should be mentioned in which nonspecific fixation reactions are found. These are hereditary syphilis and diphtheria. In Table 3 are given the results of the tests on children with these two diseases in which it will be seen that almost one-third of the cases have reacted to the complement fixation test for tuberculosis. The syphilis cases all showed a strongly positive Wassermann reaction although fifteen others which had been treated until the Wassermann was negative failed to give a positive fixation test for tuberculosis. Some of the older children had positive tuberculin skin tests but none had demonstrable evidence of tuberculosis. There is no such relation of positive fixation to age as is found in the tuberculosis cases and several children in the first year of life gave positive fixation reactions, a finding quite at variance with the results in tuberculosis. From these observations it seems evident that children with hereditary syphilis and a strongly positive Wassermann reaction may give a positive complement fixation test for tuberculosis in the absence of any tuberculosis in such children. The explanation of this nonspecific fixation is not clear but it seems likely that in children with a high concentration of syphilitic antibodies in the blood, the tubercle antigen has an action similar to the other nonspecific lipoid antigens used in the Wassermann test. The antibodies giving the Wassermann reaction are usually present in considerably higher concentration in children with hereditary syphilis than in adults with the acquired form of the disease. This has been determined by titrating the minimal fixing dose of serum from a number of cases.

TABLE 3.—RESULTS OF COMPLEMENT FIXATION FOR TUBERCULOSIS IN CONGENITAL SYPHILIS AND DIPHTHERIA

Age in Years	Syphilis		Diphtheria	
	Number Tested	Fixation Positive	Number Tested	Fixation Positive
0– 1	14	3	..	..
1– 2	9	0	..	..
2– 4	9	2	8	2
4– 6	7	2	10	3
6– 9	11	3	20	6
9–12	11	7	8	4
12–15	14	4	3	0
Total	75	21	49	15
		28%		30.6%

The relatively high percentage of diphtheria cases giving a positive fixation test for tuberculosis was quite unexpected. These tests were made on children after the acute symptoms of the disease had subsided and on others suffering from postdiphtheritic polyneuritis. All cases had negative skin tuberculin tests, except seven which

included only one of those giving positive fixations. In none of the group could any evidence of tuberculosis be found so that the negative reactions appear definitely nonspecific. That the presence of such fixing bodies in the blood is probably transient is indicated by observations made on two children who had negative fixations before and six months after the diphtheria with strongly positive reactions during the attack. All patients had been given antitoxin and these children were the only ones studied in whom a foreign protein had been injected. In a previous paper [4] it was shown that highly immune serums may give a nonspecific fixation with other antigens if relatively large amounts (0.1 c.c.) of serum are used. Whether the nonspecific fixation noted after diphtheria is in any manner associated with the serum injection or whether it is due to a high concentration of specific immune substances of the diphtheritic infection, has not been determined.

TABLE 4.—Complement Fixation Tests for Tuberculosis in Children With No Clinical Tuberculosis and With Negative Wassermann Reactions (No Diphtheria Included)

Age in Years	Skin Tuberculin Test Negative		Skin Tuberculin Test Not Done		Skin Tuberculin Test Positive	
	Total Number	Fixation Positive	Total Number	Fixation Positive	Total Number	Fixation Positive
0– 1	43	..	51	..	...	...
1– 2	47	..	17	..	1	...
2– 4	63	1	51	2	7	1
4– 6	68	1	60	..	12	...
6– 9	139	7	112	8	40	8
9–12	108	5	98	9	41	8
12–15	88	5	68	8	27	4
Total	556	19 3.4%	457	27 5.9%	128	21 16.6%

Table 4 shows the results of the complement fixation test for tuberculosis in children with no evidence of clinical tuberculosis. No cases of syphilis with positive Wassermann reactions are included and no cases of diphtheria or postdiphtheritic paralysis. The group is composed of normal children and those with the common ailments of infancy and childhood. In infants, the various nutritional disorders, rickets, tetany, scurvy, congenital heart disease, bronchitis, pneumonia, otitis, stomatitis, iliocolitis, poliomyelitis, pyelitis, meningitis and sepsis formed the bulk of the cases. Among the older children groups of cases were examined with the infectious exanthemas, typhoid fever, malaria, pertussis, rheumatic fever, influenza, pneumonia, meningitis, mumps, osteomyelitis, encephalitis and other acute infections, as well as chronic diseases such as nephritis, cardiac decompensation, leukemia, tumors, Banti's disease, epilepsy, diabetes mellitus, diabetes insipidus, chronic arthritis, and in fact all the various

medical and surgical conditions seen in a general pediatric service during a period of two years. In none of these diseases was there found any tendency to react positively to the fixation test. As may be seen from Table 4, a certain number of children, however, did give positive reactions. A rather small percentage (3.4) of those with negative skin tuberculin tests gave positive fixations. The diagnosis in these nineteen cases may be of some interest.

There were four cases of chronic pneumonia, three of chronic cervical adenitis, three of chronic bronchitis and malnutrition, two of mental deficiency and one each of pneumonia, typhoid fever, malaria, chronic endocarditis, chronic nephritis, hypertrophied tonsils and simple malnutrition. In those cases with positive fixations in which the skin tuberculin tests were positive or not performed, it is possible that some focus of active tuberculosis was present although none was detected. The obvious difficulties in recognizing clinically every such case needs no comment, and it is of interest in this connection that of the children without clinical evidence of tuberculosis, five times as many with positive skin tuberculin tests gave positive fixation reactions as those with negative skin tests.

DISCUSSION

Several features of some interest have been observed in the series of complement fixation tests for tuberculosis. In manifest tuberculosis, there has been a striking relation between the age of the child and a positive fixation reaction. More than 80 per cent. of those over 6 years of age gave positive reactions, a proportion similar to that found in adults,[4] while none in the first year reacted positively to the test. From the second to the sixth year gradually increasing numbers of children develop fixing antibodies. There are two possible factors in the failure of infants and young children to develop complement-fixing substances in the blood. The duration of the infection may influence their formation and the younger children may have had the infection too short a time for the development of such antibodies. This explanation seems less likely than that young animals may form antibodies much less readily than older ones. The Wassermann reaction in syphilis is not a specific fixation, and consequently there is no true analogy, but even here infants with hereditary syphilis may give a negative Wassermann at birth and not develop a positive one until several months later. The absence of fixing bodies in tuberculosis of infants and in a considerable proportion of younger children may have some relation to the very rapid spread of the disease at this time of life which is commonly observed, since the inability to form fixing antibodies may be associated with a lack of power to form other protective antibodies.

The absence of complement-fixing antibodies in young children, however, has little importance in the question of diagnosis since it is at this age that the tuberculin skin tests are of greatest value in calling attention to an active infection. In older children, on the other hand, the skin tests do not always indicate the presence of an active tuberculous process, and it is here that the complement fixation test is of particular value, because of the high proportion of tuberculous children who give a positive reaction.

In a large number of children the tuberculous infection, usually of the tracheobronchial glands, is slight in extent and the process is masked by the relatively insignificant clinical signs that are commonly present. There seems little doubt, however, that in these cases the infection is pathologically active since there is sufficient continuous absorption from the tuberculous focus to produce complement-fixing antibodies. The children of this masked tuberculosis group give positive complement fixation reactions in the same proportion as those with manifest tuberculosis. The test is consequently of great aid in calling attention to this rather common and frequently overlooked type of tuberculosis in children. Additional evidence that a positive fixation test is associated with a pathological activity of the tuberculous process if furnished by the relatively small number of children with clinically healed tuberculosis who give positive reactions.

Certain nonspecific reactions may occur in children with congenital syphilis and a strongly positive Wassermann test, and also in cases of diphtheria for several months after the acute attack. This should be borne in mind to prevent misinterpretation of positive fixation reactions in these conditions. In more than one thousand other cases in which no clinical tuberculosis could be demonstrated, positive fixation reactions were found in less than 5 per cent. The great difficulty in absolutely excluding tuberculous infection by present diagnostic methods suggests that some of these apparent "false positives" may not be quite free of the disease.

The test has proved of considerable value not only in calling attention to cases of tuberculosis without well defined clinical signs, but in making a decision regarding the presence of active tuberculous foci in children exposed to the disease and also in following the course of a healing lesion. The complement fixation reaction, however, must not be considered a relatively easy and infallible method of diagnosing an active tuberculous process. It is of most value when used as an aid to a careful and complete physical examination of the patient. The results show that a positive fixation reaction is associated in a large majority of cases with a tuberculous lesion that is pathologically if not clinically active, and consequently any patient giving a positive reaction should not be considered free from active tuberculosis without a thorough study.

PRECIPITINS TO EGG WHITE IN THE URINE OF NEW-BORN INFANTS *

C. G. GRULEE, M.D., and B. E. BONAR, M.D.

CHICAGO

In 1904, Ganghofer and Langer [1] carried out some experiments on animals to test the permeability of the intestinal wall to foreign albumin. Their examinations consisted of precipitin reactions on the blood of new-born animals. They found that in young dogs or other animals previous to the sixth day of life, the precipitin reactions to foreign albumin were positive although the quantity of albumin consumed was very small. Their experiments were carried out on dogs, cats, rabbits and kids.

In 1913, Lust [2] attempted to determine the presence of egg white in the urine of infants. For this purpose he used precipitin serum, which gave the reaction in dilution of 1 : 100,000; oftentimes of 1 : 1,-000,000. He used egg albumin because it was much easier to recognize by the precipitin reaction. In his first series of ten infants suffering from various types of nutritional disturbances, he found that while the precipitin reaction was present in the blood in none of his cases, he was able to obtain four positive results in the urine. Against the objection that egg white may be irritating to the intestinal canal after use in large quantities, he states that for the test of permeability one does not have to take into consideration any slight irritation which may occur from the single ingestion.

In a series of twelve normal infants which he examined, he was **able to obtain no reactions,** even though the dosage of the egg was increased up to 55 and 60 gm. Among nine infants with acute dyspepsia, however, treated in the same manner, there were three positive reactions. In seven cases of severe dyspepsia, intoxication and colitis, in all but one there were definite reactions. Age seemed to play no rôle, nor did the quantity, the dose of the egg white being at least ten times less than to the normal individual. He thinks, therefore, that the physical processes in the bowel are not dissimilar from those obtained by Mayerhofer and Pribam [3] in their experiments on the intestines of infants dead of acute and of chronic nutritional disturbances.

1. München. med. Wchnschr. **51**:1497, 1904.
2. Jahrb. f. Kinderh. **77**:243, 383, 1913.
3. Wien. klin. Wchnschr. **22**:875, 1909.

In nineteen cases of chronic nutritional disturbances he was able to recognize egg white in the urine in twelve; the intensity of the reaction, however, was far below that obtained in the acute cases. During the reparative stage there seemed to be a gradual resumption of function on the part of the intestines. It would seem from this that even though the intestinal wall in these cases allows heterologous albumins to pass, no irreparable damage is produced by this. His examinations for cow's milk protein were unsatisfactory. In only one case out of seventeen was it possible to recognize the albumin. Examinations on animals, however, were more successful. Excretion began usually after two or three hours, increased from then on, and went slowly after six or eight hours. In no case was it possible to obtain a reaction after twenty-four hours. The quantity of albumin was never sufficient to be determined chemically.

Hahn [4] confirmed Lust's work, using diphtheria antitoxin. He was not able to obtain any reaction in intestinally healthy infants, but was in those with nutritional disturbances when large quantities of antitoxin were used.

Lawatschek [5] examined by the precipitin reaction the urine of the new-born for egg albumin. He gave at least the white of half an egg at one time; the urine was collected and examined, immediately. In four of twenty-one cases there was a pronounced reaction for egg albumin in the urine (six of the cases were dyspeptic infants). The largest number of reactions occurred on the second, eighth and ninth days. After the tenth day the reactions were weaker. In the older infants his results corresponded very closely to those of Lust.

Hayashi [6] used the precipitin reaction on the urine in testing the permeability of the infant's intestinal wall for egg albumin, and also examined the urine for disaccharids. The reactions were obtained in from two and one-half to eight and one-half hours after ingestion. The youngest child was 1¼ months old, and the ages varied from that up to 12 months. Normal children required from 12 to 30 gm. of egg white per kilogram of body weight.

A second series of eleven cases, of which five were eczemas, the patients being from 2 to 8 months of age, reactions occurred in from two to seven hours and were obtained by using from 12 to 18 gm. In five cases following acute gastro-intestinal disturbances the amount used was from 10 to 12 gm. In a series of sixteen cases in which he tested the permeability, not only of egg albumin but also of cane sugar and milk sugar, he found that the quantity of egg albumin per

4. Jahrb. f. Kinderh. **77**:405, 1913.
5. Prag. med. Wchnschr. **39**:185, 1914.
6. Monatschr. f. Kinderh. **12**:749, 1914.

kilogram of body weight necessary for its recognition in the urine was from 10 to 20 gm., of the cane sugar from 3 to 8 gm., and of the milk sugar from 2 to 8 gm.

Modigliani and Benini [7] examined the blood of infants for precipitin reaction to cow's milk casein. They prepared a rabbit serum for this purpose. Their first series consisted of ten children, aged from 3 to 9 months. There were two positive reactions in the nourishment disturbed infants, one a chronic and the other an acute reaction. In their second series of nineteen children, aged from 4 days to 4 months, they had seven positive and three doubtful reactions. Of the seven positive reactions, four were acute, and three in cases of chronic nutritional disturbances. Of the three doubtful reactions one child was normal, one was suffering with acute, and the third with chronic nutritional disturbance.

In a 4 day old normal infant there was no reaction, and in a 10 day old infant with acute disturbance the reaction was doubtful.

Schloss and Warthin,[8] in examining the gastro-intestinal tract of infants for undigested protein, used egg white for this purpose. The white of one or two eggs was given and the urine collected for six hours thereafter. In fourteen normal infants they obtained two positive results. In seven infants with mild gastro-enteric dyspepsia two showed positive reactions; three out of four children with moderately severe symptoms gave a positive reaction; and six with severe symptoms all showed positive reactions at some time during the disease. In six cases of eczema the results were positive in three.

The present investigations were undertaken in order to determine the permeability of the intestinal tract of the new-born infant to egg albumin. The cases were, so far as possible, routine cases taken from the service at the hospital. They differed in no way from cases of a like sort which we had been observing in the hospital for several years. They were not selected cases. In order that the conditions under which these children lived might show no variation from those which had been observed previously, no special change was made in the routine treatment of the case. The only way in which the care of these infants differed from that of previously observed cases was that the children were given the egg albumin in a manner to be described later and specimens of the urine were collected so far as possible daily. No attempt was made to obtain twenty-four-hour specimens. Single specimens were usually obtained by the night nurse, the so-called morning specimen. The egg white was given in a 2 per cent. solution (10 c.c. to 500 c.c. of water).

7. Policlinico, Sez. Med. **21**:540, 1914.
8. Am. J. Dis. Child. **11**:342 (April) 1916.

TABLE 1.—Results of Examination From First to Thirteenth Day After Feeding Albumin Water

Number	Case No.	Weight	C.c. Albumin Water	Gm. Albumin	Gm. per Kg.	Reaction	Number	Case No.	Weight	C.c. Albumin Water	Gm. Albumin	Gm. per Kg.	Reaction
1	132446						7	132673					
	1st day	3,408	56	1.12	0.33	—		1st day	4,656	64	1.28	0.18	—
	2d day	3,280	32	0.64	0.20	—		2d day	4,496	112	2.24	0.50	—
	3d day	3,056	32	0.64	0.21	—		3d day	4,400	40	0.80	0.18	—
	4th day	3,152	96	1.92	0.62	—		4th day	4,432	48	0.96	0.22	—
	5th day	3,328	44	0.88	0.27	—		5th day	4,496	88	1.76	0.40	0
	6th day	3,360	112	2.24	0.68	—		6th day	4,544	112	2.24	0.50	0
	7th day	3,456	80	1.60	0.47	—		7th day	4,528	64	1.28	0.28	0
	8th day	3,408	96	1.92	0.56	—		8th day	4,496	80	1.60	0.36	±
	9th day	3,264	104	2.08	0.65	—		9th day	4,560	32	0.64	0.14	++
	10th day	3,264	52	1.04	0.33	++		10th day	4,560	16	0.32	0.07	—
2	132531						8	132695					
	1st day	3,776	32	0.64	0.17	—		1st day	3,504	32	0.64	0.18	—
	2d day	3,664	56	1.12	0.31	—		2d day	3,248	48	0.96	0.30	0
	3d day	3,680	96	1.92	0.53	—		3d day	3,216	64	1.28	0.40	0
	4th day	3,632	56	1.12	0.31	—		4th day	3,248	104	2.08	0.65	0
	5th day	3,696	64	1.28	0.36	—		5th day	3,248	64	1.28	0.40	+
	6th day	3,712	64	1.28	0.35	—		6th day	3,296	72	1.44	0.44	+++
	7th day	3,760	56	1.12	0.30	++		7th day	3,344	48	0.96	0.29	0
	8th day	3,744	24	0.48	0.13	0		8th day	3,376	48	0.96	0.29	++
	9th day	3,728	48	0.96	0.26	—		9th day	3,392	32	0.64	0.19	+
	10th day	3,760	50	1.12	0.30	—	9	133056					
3	132532							1st day	3,456	0	0.00	—	0
	1st day	3,232	32	0.64	0.20	—		2d day	3,328	64	1.28	0.39	0
	2d day	3,264	80	1.60	0.50	—		3d day	3,296	64	1.28	0.40	0
	3d day	3,168	128	2.56	0.82	—		4th day	3,280	48	0.96	0.30	0
	4th day	3,200	80	1.60	0.50	—		5th day	3,344	64	1.28	0.39	0
	5th day	3,216	64	1.28	0.40	—		6th day	3,344	80	1.60	0.50	+
	6th day	3,296	120	2.40	0.73	—		7th day	3,408	40	0.80	0.24	0
	7th day	3,312	112	2.24	0.68	—		8th day	3,440	64	1.28	0.38	—
	8th day	3,280	68	1.36	0.41	—		9th day	3,440	64	1.28	0.38	0
	9th day	3,408	128	2.56	0.75	++		10th day	3,488	—	—	—	
	10th day	3,392	64	1.28	0.38	—	10	133161					
4	132631							1st day	3,808	16	0.32	0.04	0
	1st day	4.032	48	0.96	0.24	—		2d day	3,616	32	0.64	0.18	0
	2d day	3,952	56	1.12	0.29	—		3d day	3,520	40	0.80	0.23	—
	3d day	3,856	104	2.08	0.55	—		4th day	3,600	28	0.56	0.16	—
	4th day	3,824	96	1.92	0.51	—		5th day	3,728	64	1.28	0.35	0
	5th day	3,872	88	1.76	0.46	+		6th day	3,872	56	1.12	0.30	0
	6th day	3,920	48	0.96	0.25	++		7th day	3,888	32	0.64	0.16	0
	7th day	3,936	56	1.12	0.29	0		8th day	3,952	52	1.04	0.26	±
	8th day	3,968	80	1.60	0.41	—		9th day	3,968	88	1.76	0.45	—
	9th day	4,048	80	1.60	0.40	—		10th day	—	16	0.32	—	0
	10th day	4,048	—	—	—	—	11	133211					
5	132588							1st day	3,696	8	0.16	0.04	—
	1st day	4,096	32	0.64	0.34	—		2d day	3,636	16	0.32	0.09	—
	2d day	3,968	80	1.60	0.41	—		3d day	3,424	48	0.96	0.28	—
	3d day	3,888	80	1.60	0.41	—		4th day	3,392	0	0.00	—	—
	4th day	4,000	80	1.60	0.40	—		5th day	3,440	48	0.96	0.28	+
	5th day	4,016	56	1.12	0.28	0		6th day	3,456	40	0.80	0.23	0
	6th day	4,064	56	1.12	0.28	0		7th day	3,472	68	1.36	0.40	0
	7th day	4,112	32	0.64	0.12	—		8th day	3,440	64	1.28	0.38	—
	8th day	4,144	72	1.44	0.35	0		9th day	3,504	48	0.96	0.25	0
	9th day	4,176	112	2.24	0.55	±		10th day	3,456	56	1.12	0.33	0
	10th day	4,144	32	0.64	0.15	—		11th day	3,536	16	0.32	0.09	—
6	132654						12	133254					
	1st day	3,680	64	1.28	0.30	—		1st day	4,320	8	0.16	0.10	—
	2d day	3,536	80	1.60	0.46	—		2d day	4,112	64	1.28	0.31	0
	3d day	3,376	64	1.28	0.39	—		3d day	4,048	32	0.64	0.16	—
	4th day	3,340	48	0.96	0.29	++		4th day	3,856	96	1.92	0.51	—
	5th day	3,472	64	1.28	0.38	+		5th day	3,808	104	2.08	0.55	+
	6th day	3,552	80	1.60	0.46	+		6th day	3,904	80	1.60	0.41	0
	7th day	3,568	96	1.92	0.55	0		7th day	3,888	136	2.72	0.70	+
	8th day	3,632	48	0.96	0.27	0		8th day	3,984	64	1.28	0.32	—
	9th day	3,696	80	1.60	0.43	0		9th day	4,048	128	2.56	0.64	0
	10th day	3,792	48	0.96	0.25	++		10th day	4,096	168	3.36	0.82	0
	11th day	3,584	56	1.12	0.31	+		11th day	4,112	96	1.92	0.47	+
	12th day	3,760	16	0.32	0.09	0		12th day	4,176	160	3.20	0.76	0
	13th day	3,744	80	1.60	0.43	+		13th day	4,192	16	0.32	0.08	—

Number	Case No.	Weight	C.c. Albumin Water	Gm. Albumin	Gm. per Kg.	Reaction	Number	Case No.	Weight	C.c. Albumin Water	Gm. Albumin	Gm. per K_j	Reaction
13	133297							9th day	4,272	32	0.64	0.05	0
	1st day	3,424	16	0.32	0.10	0		10th day	4,304	32	0.64	0.15	0
	2d day	3,312	32	0.64	0.19	0		11ht day	4,384	0	0	0	0
	3d day	3,168	48	0.96	0.31	0		12th day	4,304	24	0.48	0.11	0
	4th day	3,168	48	0.96	0.31	±/0		13th day	4,368	24	0.48.	0.11	0
	5th day	3,280	56	1.12	0.38	0							
	6th day	3,296	40	0.80	0.24	0	19*	132996					
	7th day	3,264	64	1.28	0.40	—		1st day	3,200	16	0.32	0.10	0
	8th day	3,296	48	0.96	0.28	—		2d day	2,944	36	0.72	0.24	0
	9th day	3,344	72	1.44	0.44	0		3d day	2,880	0	0.00	—	0
	10th day	3,328	—	—	—	—		4th day	2,912	16	0.32	0.11	0
								5th day	3,072	48	0.96	0.32	0
14	133324							6th day	3,152	48	0.96	0.31	0
	1st day	4,240	0	0.00	—	—		7th day	3,168	16	0.32	0.10	—
	2d day	4,096	16	0.32	0.08	—		8th day	3,184	36	0.72	0.23	0
	3d day	3,888	28	0.56	0.14	—		9th day	3,912	40	0.80	0.27	—
	4th day	3,760	104	2.08	0.56	0		10th day	3,360	24	0.48	0.15	0
	5th day	3,712	96	1.92	0.52	0		11th day	3,328	32	0.64	0.20	0
	6th day	3,792	72	1.44	0.40	0		12th day	3,392	32	0.64	0.20	—
	7th day	3,872	96	1.82	0.51	+							
	8th day	3,920	64	1.28	0.33	±	20	133286					
	9th day	3,920	64	1.28	0.33	—		1st day	3,728	16	0.32	0.08	0
	10th day	3,936	80	1.60	0.41	0		2d day	3,584	56	1.12	0.31	—
	11th day	3,984	64	1.28	0.30	—		3d day	3,344	48	0.96	0.29	0
	12th day	3,888	0	0.00	0.00	0		4th day	3,200	40	0.80	0.22	0
	13th day	3,824	32	0.64	0.17	—		5th day	3,280	80	1.60	0.49	0
								6th day	3,376	32	0.64	0.19	0
15	132884							7th day	3,360	112	2.24	0.68	0
	1st day	3,536	0	0.00	—	0		8th day	3,328	64	1.28	0.30	0
	2d day	3,456	0	0.00	—	—		9th day	3,408	96	1.92	0.57	0
	3d day	3,344	56	1.12	0.34	0		10th day	3,456	64	1.28	0.37	0
	4th hday	3,312	32	0.64	0.19	0		11th day	3,424	40	0.80	0.24	0
	5th day	3,376	44	0.88	0.27	0		12th day	3,504	32	0.64	0.18	—
	6th day	3,424	32	0.64	0.19	+							
	7th day	3,472	72	1.44	0.34	+	21†	133325					
	8th day	3,504	8	0.16	0.05	0		1st day	3,856	16	0.32	0.09	—
	9th day	3,520	40	0.80	0.23	0		2d day	3,760	32	0.64	0.14	—
	10th day	3,552	16	0.32	0.09	—		3d day	3,680	48	0.96	0.27	±
								4th day	3,648	48	0.96	0.27	+
16	132901							5th day	3,664	32	0.64	0.18	—
	1st day	3,296	16	0.32	0.10	0		6th day	3,680	80	1.60	0.41	—
	2d day	3,232	48	0.96	0.30	0		7th day	3,712	128	2.56	0.69	0
	3d day	3,200	32	0.64	0.20	0		8th day	3,744	64	1.28	0.35	0
	4th day	3,216	48	0.96	0.30	—		9th day	3,744	48	0.96	0.26	0
	5th day	3,232	76	1.52	0.47	—		10th day	3,744	32	0.64	0.17	0
	6th day	3,280	32	0.64	0.19	0		11th day	3,840	16	0.32	0.09	—
	7th day	3,312	32	0.64	0.19	++							
	8th day	3,344	8	0.16	0.05	0	22	133462					
	9th day	3,424	48	0.96	0.28	—		1st day	3,232	8	0.16	0.05	—
	10th day	3,328	—	—	—	—		2d day	3,200	56	1.12	0.35	—
								3d day	3,040	48	0.96	0.32	—
17	133157							4th day	2,944	48	0.96	0.33	0
	1st day	3,184	16	0.32	0.10	0		5th day	2,976	56	1.12	0.39	—
	2d day	3,088	8	0.16	0.05	0		6th day	3,024	36	0.72	0.24	0
	3d day	3,008	32	0.64	0.21	0		7th day	3,088	72	1.44	0.46	0
	4th day	3,120	16	0.32	0.10	—		8th day	3,120	48	0.96	0.31	0
	5th day	3,136	48	0.96	0.31	+		9th day	3,104	32	0.64	0.21	—
	6th day	3,088	64	1.28	0.43	—		10th day	3,120	16	0.32	0.10	—
	7th day	3,184	64	1.28	0.40	0		11th day	3,136	32	0.64	0.21	—
	8th day	3,200	48	0.96	0.30	0							
	9th day	3,264	48	0.96	0.30	—	23	133517					
	10th day	3,280	48	0.96	0.29	+		1st day	4,544	32	0.64	0.14	—
								2d day	4,256	80	1.60	0.38	—
18	132653							3d day	4,096	80	1.60	0.39	—
	1st day	4,720	16	0.32	0.07	—		4th day	4,032	40	0.80	0.20	—
	2d day	4,608	64	1.28	0.28	—		5th day	4,160	64	1.28	0.31	0
	3d day	4,336	72	1.44	0.34	—		6th day	4,192	44	0.88	0.21	0
	4th day	4,112	96	1.92	0.48	—		7th day	4,272	72	1.44	0.34	—
	5th day	4,104	144	2.88	0.70	—		8th day	4,312	96	1.92	0.45	—
	6th day	4,096	80	1.60	0.40	—		9th day	4,336	64	1.28	0.30	—
	7th day	4,080	64	1.28	0.31	0		10th day	4,384	48	0.96	0.22	—
	8th day	4,176	76	1.52	0.37	0		11th day	4,336	32	0.64	0.15	—

* Pyelocystitis.　　　　　† Birth injury.

Instead of these children being given plain water between nursings, they were given this weak egg albumin solution, and the quantity of the water thus taken by the infant recorded by the nurse. The precipitin reactions were carried out as mentioned in a previous investigation [9] using an antieggwhite rabbit serum of at least 50,000.

As shown in Table 1, 136 specimens of urine were examined. These were taken from twenty-three different infants. Thirty-three specimens, or 24.3 per cent., gave a positive reaction, but of these eighteen, or approximately 75 per cent., had at one time or another shown one or more positive reactions.

TABLE 2.—DISTRIBUTION OF REACTIONS

Day of Life	Number of Specimens	Positive
1	8	0
2	8	0
3	6	0
4	10	3
5	17	7
6	14	5
7	18	5
8	15	4
9	12	4
10	12	8
11	5	2
12	4	0
13	2	0

TABLE 3.—RESULTS OF EXAMINATION OF CONTROLS

Day of Life	Number of Specimens	Day of Life	Number of Specimens
2	4	8	4
3	3	9	2
4	2	10	4
5	6	11	1
6	3	12	1
7	4		

The first positive reactions were found in the urine obtained on the fourth day of life. The period from the fourth to the eleventh day showed approximately the same proportion of positive reactions for each day. No reactions were obtained after the eleventh day but the number of cases was so small as to take away any significance which might otherwise be attached to this statement.

At no time did the amount of albumin per kilogram for twenty-four hours exceed 0.82 gm. Of the positive reactions the lowest was obtained when the infant received 0.14 gm. per kilogram; and the highest at 0.75 gm.

For controls, forty-one specimens were obtained from seventeen different patients. In no instance was a positive reaction obtained (Table 3).

---

9. Hektoen and Grulee: Am. J. Dis. Child. **18**:1 (July) 1919.

An observation which may be of some interest is that in six of the cases, sixteen stools had been examined for egg precipitin reaction (these were cases reported in a former paper).[10] In no instance was there a negative reaction in the stool with a positive reaction in the urine. In one case the stool was positive but the urine was negative.

From these examinations it would seem fair to conclude that the intestinal wall of the new-born infant from the fourth to the tenth day, inclusive, is permeable to small quantities of egg white which can be determined by the precipitin reaction in the urine. With these findings it would seem likely that this is not a reaction of specific cases but is a general characteristic of that period of life. The results suggest an explanation of sensitization to egg and other foreign albumin.

---

10. Grulee: Am. J. Dis. Child. **20**:15 (July) 1920.

BLOOD VOLUME IN INFANTS ESTIMATED BY THE VITAL DYE METHOD *

WILLIAM PALMER LUCAS, M.D.,

AND

BRADFORD FRENCH DEARING, M.D.

SAN FRANCISCO

This report is part of a study which is now being carried on in the pediatric department on the problem of the anemias of infancy and childhood. Many studies have been made in this field but most of the work so far done has reference mainly to the blood picture, studies relating to the differential count of the white blood cells, the study of the red blood cells, their number and fragility and to the percentage of hemoglobin; in many instances the postmortem findings are added to these studies of the cells and hemoglobin. All these studies are valuable and have their place in the problem of the anemias but so far they have led to little more than an unsatisfactory classification of the anemias. Even as regards classification there is much confusion and very little has been ascertained as to the etiology of the various anemias which occur so frequently during infancy and childhood. Today we can do little more than divide anemias into primary and secondary groups. We know little as to the specific causes of these anemias. We know the end results well but what has brought about these results we know little of and it would seem that we are likely not to go much further in our understanding of these blood conditions unless we attack the problem from a somewhat different standpoint.

During the past few years a great deal of experimental work has been done on blood, regarding it as an organ. Blood regeneration following certain measures used to injure or modify the functioning of the bone marrow and spleen, as certain bacterial toxins, certain chemical poisons as benzol and saponin or the administration of over exposure to roentgen-ray and radium, have been studied carefully.[1] These investigations have thrown a good deal of additional light on many of the functions of the blood and blood forming organs. The rate of regeneration of the red blood cells is fairly definitely known. The capacity to regenerate following certain of these procedures has also been carefully investigated and we have data now of considerable importance on these points.

1. Whipple, et al: Series of articles on Blood Regeneration Following Simple Anemias, Am. J. Physiol. **52**:151, 167, 206, 236, 263, 1920.

The many studies on coagulation have differentiated the various factors which enter into this complex function. From the results of these studies we are now able to group various types of hemorrhagic conditions, according to which factor, salt, prothrombin, platelets, fibrinogen, antithrombin, is disturbed. By these means our understanding of these puzzling conditions has been greatly clarified and our measures for combating or favorably effecting them has been materially advanced.[2] The close relationship of some of these hemorrhagic conditions, such as purpura hemorrhagica, to the group of the little understood primary anemias, aplastic anemias, has been pointed out by Minot.[3]

Equally important are the studies on pigment production and destruction in the blood for a better understanding of the functions of blood considered as an organ. The part the liver plays on this pigment formation has been carefully worked out by Whipple and his associates [4] in their anemia studies on bile and plood pigment. They have pointed out the part the liver plays in pigment formation. So far, clinically, little or no attention has been paid to hemoglobin beyond the estimation of the percentage of hemoglobin found in various blood disturbances. Unfortunately, most of the numerous reports are based on inaccurate methods of estimating hemoglobin and this notwithstanding the fact that Van Slyke,[5] and Palmer [6] and more recently Robscheit [7] have pointed out the inaccuracies of older methods and the latter has described a simple accurate adaptation of their methods for clinical use.[7] They have shown that the estimation of hemoglobin by the Tallqvist methods and others now in common clinical use have an inaccuracy of from 15 to 30 per cent. which in some cases runs as high as 50 per cent. from a correct estimation of hemoglobin as done by the Palmer modification.

Before one can even begin to make a study of the anemias there are certain questions that must be definitely answered, questions for which we have at present no normal standards. It is first necessary to obtain figures on which to base our studies. We have been fortunately placed for making these studies on anemias of infancy and childhood because for the past three years researches on these problems have been in progress and are now in progress at the Hooper Foundation for Medical Research.

2. Hurwitz, S. H., and Lucas, W. P.: A Study of the Blood in Hemophilia, Arch. Int. Med. **17**:543 (April) 1916.

3. Minot, G. R.: Arch. Int. Med. **19**:1062 (June) 1917.

4. See Ref. 1.

5. Van Slyke, D.: J. Biol. Chem. **33**:127, 1918.

6. Palmer: J. Biol. Chem. **41**:209, 1920.

7. Robscheit, F. S.: J. Biol. Chem. **41**:209, 1920.

One of the first of these questions to be settled is that of a normal blood volume in infancy and childhood. It is needless to point out that we cannot go very far in any comprehensive understanding of the blood as an organ without some idea as to the volume of blood normally in circulation, its normal variations at different periods and under varying conditions of nutrition and growth. The first point we have attempted to arrive at any conclusion on is the normal blood volume in infancy. This paper deals mainly with the normal variations during the first year. We have only a few examples of blood volumes in infants suffering from some form of secondary anemia.

HISTORICAL

Keith, Rowntree and Geraghty [8] first used the dye method for estimating the blood volume. In their studies they used vital red and demonstrated that the normal blood volume for adults is about 8.8 per cent. or 1-11.4 of the body weight. Unfortunately, their supply of dye was limited and on account of the war they were unable to procure more to carry on their studies.

For several years Dr. Herbert M. Evans has been studying the various dyes in his investigations on vital tissue staining. From his work he was able to suggest that brilliant vital red would most probably be the dye best suited for blood volume studies. Dr. Whipple and his associates have tested this dye out in many hundreds of experiments and have found that it answers the requirements for a satisfactory dye. First, because it is nontoxic when injected intravenously, even in large doses fifteen times that used in the estimation of plasma volume. Second, this dye is not taken up by any of the red blood cells or tissues but remains for a comparatively long time in the plasma but the ultimate fate of the dye is not known. Third, it can easily and accurately be determined by colorimetric methods. The use of this dye in dogs has shown that the normal healthy growing dog has an average blood volume of 10.1 per cent. body weight. So far as we know this method has not been applied to infants or children. During early infancy this method can be easily carried out by using the longitudinal sinus, and thanks to the Goldbloom [9] block we have a safe device for the accurate injection of dye. Without this block the work would have been much more difficult, in fact we started some of these studies before we were able to secure this simple device and we can testify that it has facilitated our work and made us feel far more confident in persisting with the repeated injections of the dye on so many cases. In working with new-born infants this block is indispensable. The sinus was used by us in all

8. Keith, Rowntree and Geraghty: Arch. Int. Med. **16**:547 (Sept.) 1915.
9. Goldbloom, A.: Am. J. Dis. Child. **16**:388 (Sept.) 1918.

our studies, except the few we have done in children over 18 months old. In these older children we have used either the jugular veins or the veins at the elbow, the latter where they are large enough, we have found easier to work with than the jugular veins, for as will be seen there is a certain minimum of manipulation necessary in changing syringes which makes it difficult to use the neck veins.

<div align="center">PROCEDURE</div>

Ten c.c. of blood are withdrawn into a Record syringe which has been sterilized and thoroughly washed out with sterile salt solution. This first sample of blood is immediately discharged into an accurately calibrated 15 c.c. centrifuge tube (hematocrit tube) which contains 2 c.c. of a 1.6 per cent. solution of sodium oxalate;[7] the blood and oxalate are thoroughly mixed by inverting the tube several times so as to obviate any possible clotting. The centrifuge tube is then stoppered. From this tube the hematocrit readings are made and the serum for making the standard control dye mixture is taken. Before this first sample of blood is taken the standard amount of dye solution is drawn up into a Record syringe along with enough physiologic sodium chlorid (0.9) solution to make sure that all the dye has been taken up into the syringe from the small containing dish in which the measured amount of dye is placed.

The dye solution is a 1.5 per cent. solution and is given in the amount of 1 c.c. per 5 kg. of body weight, which gives 3 mg. of the dye per kilogram. The dye solution is injected into the sinus, immediately after the first 10 c.c. of blood have been withdrawn, using the same needle, only changing the syringe, the dye being completely washed out by drawing blood back and forth several times into the syringe after the dye has been emptied out of the syringe into the sinus. We have found this the most convenient and satisfactory way of being sure that all the dye had been delivered into the sinus. We have had no untoward happenings while following this method. The needle is then withdrawn; exactly four minutes after the injection of this dye a clean needle is again inserted into the sinus and a sample of 16 c.c. of blood is withdrawn and discharged immediately into two petrolatum lined test tubes about equally distributed. This furnishes the plasma for the estimation of the blood plasma volume. All the tubes are now placed in the ice chest for at least half an hour, then centrifuged at 2,500 revolutions a minute for half an hour. In the hematocrit tube, (accurately calibrated centrifuge tube) the total amount of fluid is noted and the number of cubic centimeters of blood cells, red and white, are noted. This gives the total hematocrit reading when 2 c.c. is subtracted for the oxalate dilution and the hematocrit reading for the red blood cells. Five c.c. of this serum

are pipetted off and to this is added 5 c.c. of a 0.9 per cent. sodium chlorid solution and 5 c.c. aqueous dye solution. This dye solution is made up as follows: 0.5 c.c. of a 1.5 per cent. brilliant vital red is pipetted into a 100 c.c. volumetric flask which is then filled up to the mark with distilled water. This gives the standard against which is read the unknown dye colored plasma. The dye colored serum is pipetted off from the petrolatumed tube and 2 c.c. of this serum is diluted with 4 c.c. of a 0.9 per cent. sodium chlorid solution, which gives the same dilution to this serum as the standard dye solution made from patient's dye free plasma, to which has been added a known amount of dye and salt solution.

After mixing thoroughly, the standard dye-plasma solution and serum solution are allowed to stand for fifteen minutes, so that the intensity of color may be uniform. The standard dye solution is then put into the colorimetric wedge (we have used in all our work the Hellige colorimeter and have found it perfectly satisfactory. It has been tested against the Duboscq and found accurate) and each of the samples of the unknown serum dye solution is read against this. The average of three readings is taken as the color percentage of the sample.

COMPUTATION RESULTS

From the hematocrit readings the plasma per cent. and the red cell per cent. may easily be calculated—the red cell hematocrit reading is read from the hematocrit tube, taking the total hematocrit reading minus 2 and the plasma hematocrit reading by subtracting the total cell hematocrit reading from the total hematocrit reading minus 2.

$$\text{Plasma volume in c.c.} = \frac{\text{Weight in kilograms} \times 40}{\text{Average colorimetric reading}} \times 100$$

$$\text{Blood volume in c.c.} = \frac{\text{Plasma volume}}{\text{Plasma per cent.}} \times 100$$

The plasma per cent. means the per cent. of the whole blood which the plasma constitutes and is obtained by dividing the total number of cubic centimeters of oxalated plasma present in the hematocrit tube minus 2 by the total contents of the tube in cubic centimeters minus 2. The red cell per cent. is calculated from the hematocrit tube by dividing the red cell reading by the total hematocrit reading minus 2. The blood volume is divided by the body weight in kilograms which gives the blood volume in c.c. per kilograms of body weight and the percentage of blood to body weight is derived from this figure by simply pointing off one place. The pigment volume is obtained by multiplying the hemoglobin per cent. by the blood volume. This gives a valuable index of the curve of blood regeneration.

TABLE 1.—CHART A· OF THIRTY NEW-BORN INFANTS' BLOOD VOLUME ESTIMATIONS FROM TWO AND ONE-HALF HOURS TO FIFTEEN DAYS. IN MOST CASES ONLY SINGLE COMPUTATIONS FOR EACH CASE WERE MADE

No.	Age	Sex*	Birth Weight	Weight Day of Blood Volume	Total Hemat. C.c.	Plasma, per Cent.	Red Cell, per Cent.	Plasma Volume C.c.	Blood Volume C.c.	Blood per Kg. C.c.	Pigment Volume	Hb., per Cent.	Red Blood Cells	Weight Day Following Blood Volume	Disc. Weight 14th Day	Reaction	Length at Birth, Cm.	Remarks
6830	30 hrs.	♂	3,560	3,495	11.3	28.5	70.5	152	542	155	672	124	6,480,000	3,330	3,680	None	52	
6639	12 hrs.	♂	3,915	3,860	11.3	48.5	49.5	214	441	114	432	98	5,640,000	3,700	3,615	None	53	
6771	28 hrs.	♂	2,900	2,830	12.5	38.4	61.5	169	441	157	467	106	7,200,000	2,790	3,250	T 37.4	50	
6771	15 days	♀	2,900	3,270	11.3	53.0	46.0	247	465	142	348	75	....	3,250	3,250	None	50	3 minutes late, obtained blood dyed
6619	11 days	♀	2,650	2,550	11.2	50.0	49.1	170	340	133	306	90	4,290,000	2,550	2,610	T 38.5 Drowsy	49	
6786	5 hrs.	♀	3,370	3,370	11.4	34.2	63.0	184	540	160	615	114	4,730,000	3,430	3,765	None	51	
6723	8 hrs.	♀	2,710	2,710	8.1	41.3	56.5	193	469	173	483	103	....	2,510	2,675	None	50	
6820	48 hrs.	♀	3,745	3,560	12.2	44.7	54.0	264	590	165	601	102	5,080,000	3,580	3,625	Vomited dur. B.V.	52	
6785	32 hrs.	♂	3,710	3,620	11.3	42.0	57.0	263	627	173	664	106	5,050,000	3,625	4,080	None	53	
6816	24 hrs.	♂	3,390	3,470	12.2	37.3	61.4	252	676	195	770	114	....	3,535	3,790	T 37.8	52	
6628	9 days	♂	3,080	2,890	10.7	41.5	57.5	154	372	129	405	109	4,660,000	2,845	2,995	None	49	
1482	3 days	♀	3,150	3,220	9.8	42.9	56.0	156	364	116	382	105	5,644,000	3,170	3,410	None	50	
6904	3 days	♂	3,150	3,060	10.75	46.5	52.0	177	382	125			....	2,950	3,325	None	50	
6090	4 days	♀	3,420	3,410	12.0	46.3	52.5	204	440	125	354	100	5,060,000	3,320	3,550	None	53	
6712	10 hrs.	♂	3,010	3,010	12.4	45.5	53.6	160	354	122	588	108	....	3,700	3,765	None	52	
6622	4 days	♀	3,850	3,740	10.5	36.7	62.3	199	545	146	444	98	5,060,000	2,960	3,190	None	51	Died jaundiced
6310	5 days	♀	2,980	2,980	12.0	42.5	56.75	192	454	152	534	109	5,992,009	3,240	3,515	None	50	
6670	6 days	♀	3,400	3,300	11.8	42.8	56.0	209	490	149	398	109	5,420,000	3,200	3,310	None	51	
6812	15 hrs.	♂	3,275	3,275	11.75	37.8	59.5	136	361	110		109	5,140,000			None		
6801	2½ hrs.	♀	3,350	3,350	8.6	36.0	61.6	184	513	155	523	102	....	3,120	3,080	None	50	2 minutes late, obtained blood dyed
6948	14 hrs.	♀	4,465	4,460	12.25	33.0	65.3	283	857	192	899	105	....	4,390	4,280	None	53	2 minutes late
Schn.	36 hrs.	♀	3,320	3,160	10.3	40.0	58.0	204	507	161	496	98	....	3,200	.....	None	52	
Flax.	32 hrs.	♀	3,030	2,950	10.6	41.5	57.0	187	331	112	307	93	....	3,010	.....	T 37.4	49	
Turt.	26 hrs.	♀	3,325	3,230	8.8	37.5	61.5	142	378	117	359	95	4,648,000	3,290	.....	None	49	
Kan.	3 hrs.	♂	2,980	2,980	11.5	35.7	53.4	159	446	150			....	2,850	.....	None	51	
2743	6 hrs.	♂	4,130	4,180	11.75	31.0	67.0	202	595	144	702	118	5,696,000		.....	Cyanotic drg. test	56	
Tiff.	12 hrs.	♀	3,845	3,720	11.2	43.7	55.3	245	566	153	549	97	5,552,000	3,720	.....	None	54	
Carl.	49 hrs.	♂	2,800	2,950	10.5	35.7	62.8	227	635	188	857	135	5,520,000	2,950	.....	None	49	2 minutes late, obtained blood dyed
Kado.	24 hrs.	♂	2,880	2,880	10.25	30.7	67.2	170	553	192	635	115	5,464,000	2,975	.....	None	50	
Kayr.	17 hrs.	♂	3,550	3,390	10.8	51.9	46.3	188	363	107	304	84	....	3,310	.....	None	51	3 minutes late

* In this column, ♂ signifies male, and ♀ female.

TABLE 2.—CHART B: OF THIRTY NEWBORN INFANTS, BLOOD VOLUME
ESTIMATIONS FROM TWO AND ONE-HALF HOURS TO FIFTEEN
DAYS. GROUPED ACCORDING TO AGE

Age	Weight in Gm.	Total Hemat., C.c.	Plasma, per Cent.	Red Cell, per Cent.	Plasma Volume, C.c.	Blood Volume, C.c.	Blood per Kg., C.c.	Gain or Loss Before Blood Volume
3 hrs.	3,350	8.6	36.0	61.6	184	513	155	None
3 hrs.	2,980	11.5	35.7	63.4	159	446	150	None
5 hrs.	3,370	11.4	34.2	63.0	184	540	160	None
6 hrs.	4,130	11.75	31.0	67.0	202	595	144	None
8 hrs.	2,710	8.1	41.3	56.5	193	469	173	None
10 hrs.	2,890	12.4	45.5	53.6	160	354	122	None
12 hrs.	3,720	11.2	43.7	55.3	245	566	153	—120 G
12 hrs.	3,860	11.3	48.5	49.5	214	441	114	— 55 G
14 hrs.	4,460	12.25	33.0	65.3	283	857	192	None
15 hrs.	3,275	11.75	37.8	59.5	136	361	110	None
24 hrs.	3,470	12.2	37.3	61.4	252	676	195	—120 G
24 hrs.	2,880	10.25	30.7	67.2	170	553	192	—165 G
26 hrs.	3,230	8.8	37.5	61.5	142	378	117	— 95 G
28 hrs.	2,830	12.5	38.4	60.0	169	441	157	— 70 G
30 hrs.	3,495	11.3	28.0	70.5	152	542	155	— 65 G
32 hrs.	2,950	10.6	41.5	57.0	137	331	112	— 80 G
32 hrs.	3,620	11.3	42.0	57.0	263	627	173	— 90 G
36 hrs.	3,160	10.3	40.0	58.0	204	507	161	—160 G
48 hrs.	3,560	12.2	44.7	54.0	264	590	165	—185 G
49 hrs.	2,950	10.5	35.7	62.8	227	635	188	+150 G
3 days	3,060	10.75	46.5	52.0	177	382	125	— 90 G
3 days	3,150	9.8	42.9	56.0	156	364	116	— 70 G
4 days	3,740	10.5	36.7	62.3	199	545	146	—110 G
4 days	3,410	12.0	46.3	52.5	204	440	128	— 10 G
5 days	2,980	12.0	42.5	57.0	192	454	152	None
6 days	3,300	11.8	42.8	56.0	209	490	149	—100 G
9 days	2,890	10.7	41.5	57.5	154	372	129	—190 G
11 days	2,550	11.2	50.0	49.1	170	340	133	—100 G
15 days	3,270	11.3	53.0	46.0	247	465	142	+370 G
15 days	2,930	9.8	49.0	49.5	167	342	117	

TABLE 3.—CHART C: OF THIRTY NEW-BORN INFANTS, BLOOD VOLUME
ESTIMATIONS FROM TWO AND ONE-HALF HOURS TO FIFTEEN
DAYS. GROUPED ACCORDING TO WEIGHT

Weight in Gm.	Age	Total Hemat., C.c.	Plasma, per Cent.	Red Cell, per Cent.	Plasma Volume, C.c.	C.c.	Blood per Kg., C.c.	Pigment Volume	Hb.	Red Blood Cells	Weight Loss or Gain Before Blood Volume
2,550	11 days	11.2	50.0	49.1	170	340	133	306	90	4,290,000	—100 G
2,710	8 hrs.	8.1	41.3	56.5	193	469	173	483	103	....	0
2,830	28 hrs.	12.5	38.4	61.5	169	441	157	467	106	7,200,000	— 70 G
2,880	24 hrs.	10.25	30.7	67.2	170	553	192	635	115	5,464,000	
2,890	10 hrs.	12.4	45.5	53.6	160	354	122	354	100	5,060,000	—120 G
2,890	9 days	10.7	41.5	57.5	154	372	129	405	109	4,660,000	—190 G
2,950	32 hrs.	10.6	41.5	57.0	137	331	112	307	93	4,648,000	— 80 G
2,950	49 hrs.	10.5	35.7	62.8	227	635	188	857	135	5,520,000	+150 G
2,980	3 hrs.	11.5	35.7	63.4	159	446	150				
2,980	5 days	12.0	42.5	56.75	192	454	152	444	98		
3,060	3 days	10.75	46.5	52.0	177	382	125	...	...	....	— 90 G
3,150	3 days	9.8	42.9	56.0	156	364	116	382	105	5,644,000	— 70 G
3,160	36 hrs.	10.3	40.0	58.0	204	507	161	496	98	....	—160 G
3,230	26 hrs.	8.8	37.5	61.5	142	378	117	359	95	....	— 95 G
3,270	15 days	11.3	53.0	46.0	247	465	142	348	75	....	+370 G
3,275	15 hrs.	11.75	37.8	59.5	136	361	110	393	109	5,140,000	
3,300	6 days	11.8	42.8	56.0	209	490	149	534	109	5,420,000	—100 G
3,350	2½ hrs.	8.6	36.0	61.6	184	513	155	523	102		
3,370	5 hrs.	11.4	34.2	63.0	184	540	160	615	114	5,730,000	
3,390	17 hrs.	10.8	51.9	46.3	188	363	107	304	84		
3,410	4 days	12.0	46.3	52.5	204	440	125	...	...	....	— 10 G
3,470	24 hrs.	12.2	37.3	61.4	252	676	195	770	114		—120 G
3,495	30 hrs.	11.3	.28.0	70.5	152	542	155	672	124	6,480,000	— 65 G
3,560	48 hrs.	12.2	44.7	54.0	264	590	165	601	102	5,080,000	—185 G
3,620	32 hrs.	11.3	42.0	57.0	263	627	173	664	106	5,050,000	— 90 G
3,720	12 hrs.	11.2	43.7	55.3	245	566	153	549	97	5,552,000	—125 G
3,740	4 days	10.5	36.7	62.3	199	545	146	588	108	5,992,000	—110 G
3,860	12 hrs.	11.3	48.5	49.5	214	441	114	432	98	5,640,000	— 55 G
4,130	6 hrs.	11.75	31.0	67.0	202	595	144	702	118	5,696,000	
4,460	14 hrs.	12.25	33.0	65.3	283	857	192	899	105	....	—170 G

DISCUSSION

It is interesting to note the great variation of blood volume per cent. in new-born infants, which ranges from 10.7 to 19.5 per cent. of body weight and from 107 to 195 c.c. per kilogram and the pigment volume from 304 to 899 c.c. The averages for these are: blood volume per cent., 14.7; blood volume per kilogram, 147 cc.; and pigment volume 521 c.c. Another one of the interesting variations is that found between plasma volume and red cell volume. The plasma volume per cent. is small as compared with the relatively high red cell percentage. These findings are fairly constant in the new-born during the first ten days. We can ascribe no reason for these wide variations beyond the fact that the blood during the first few days is undergoing a definite adjustment to its new surroundings. We know from studies on blood proteins and blood sugars, that a similar wide variation occurs during these first few days before the normal averages are established and the blood volume undoubtedly goes through this same period of adjustment when the blood forming organs are probably called on to function independent of any assistance from the maternal circulation. Of course it is not assumed that the blood forming organs have not been functioning throughout the fetal period but certainly during the first few days there must be some very definite adjustment to be established and it is therefore not surprising to find wide individual variations with rapid changes in accommodation taking place. We all know how easily blood changes occur during this period and how difficult it is for them to right themselves when any factor intervenes to disturb in any way the blood forming organs. There does not seem to be any constant correlation between blood volume and either weight, length or age in hours or days up to fifteen days.

In the infants tested who were from 15 days to 1 year of age, there is a very definite uniformity, constant at least for individuals and the variations between individuals are very much less marked than in the first fifteen days, the extremes being from 9.0 to 12.6 per cent. and the average 10.9 per cent. There seems to be a fairly definite attempt to stabilize the blood volume during the first few months and for any given infant over a period of several months at least the blood volume apparently remains at a fairly constant level as is shown in Table 4, except where some condition has intervened which might easily be assumed to have changed the blood volume.

In the pathologic cases changes from the normal blood volume are quite striking. We do not desire to discuss these variations at this time but hope to enlarge our number of studies in time in order to be able to form a more definite idea as to the factors which effect

TABLE 4.—ELEVEN FAIRLY NORMAL INFANTS, AGED FROM FIFTEEN DAYS TO ONE YEAR

Name	Diagnosis	Age	Weight, Gm.	Total Hemat., C.c.	Plasma, per Cent.	Red Cell, per Cent.	Plasma Volume, C.c.	Blood Volume, C.c.	Blood per Kg., C.c.	Hb., per Cent.	Pigment Volume	Reaction
B. O.	Normal............	15 days	2,930	9.8	49.0	49.5	167	342	117	:	...	Temp. 38 C. then immediately normal, otherwise O.K.
	Normal............	39 days	8,350	10.7	65.4	33.6	257	393	117+	63	247	Slight loss, O.K.
		50 days	3,560	10.8	67.5	31.5	279	413	116	52	214	No reaction
B. H.	Normal............	4 mos.	5,070	9.0	61.2	37.8	357	582	115	61	354	No reaction
	Normal............	4½ mos.	5,270	10.9	60.5	38.1	364	601	114	60	360	Temp. 38.4 C.,otherwise O.K.
		5 mos.	5,190	10.0	63.5	33.5	384	605	117	50	302	No reaction
		5½ mos.	5,560	10.4	66.5	33.6	420	640	115	:	...	No reaction
B. R. H.	Normal............	9¾ mos.	7,260	9.2	63.1	35.8	519	822	113	60	493	Temp. 39.4 C., loss 90 gm., O.K.
	Normal............	10 mos.	7,470	12.3	65.8	33.3	543	825	110	52	428	Temp. 38 C., loss 30 gm., O.K.
B. S.	Hare-lip.........	4 mos.	4,940	11.7	65.75	32.5	387	589	119+	:	...	No reaction
	Cleft palate......	4½ mos.	4,910	10.0	65.5	33.5	378	576	117+	:	...	Temp. 39 C., O.K.
		6 mos.	6,290	10.75	62.0	36.8	426	687	109+	59	405	No reaction
B. T.	Feeding case......	10 mos.	6,120	8.5	62.4	37.0	371	595	97	:	...	No reaction
	Rickets...........	10¼ mos.	6,250	11.6	64.7	34.4	374	577	92	:	...	Temp. 39.2 C., vomited 9 times, O.K.
			6,300	9.8	68.4	30.6	400	585	93	:	...	No reaction
B. J.	Normal............	2½ mos.	3,760	12.05	65.0	34.1	239	367	97	:	...	No reaction
	Normal............	3 mos.	3,920	9.5	72.5	26.3	275	380	97	:	...	No reaction
B. V.	Spasmophilia......	7 mos.	5,350	9.0	64.0	35.0	362	566	106	:	...	Loss 140 gm., O.K.
	Rickets...........	7½ mos.	5,600	10.55	66.0	33.2	361	546	97	:	...	Loss 40 gm., O.K.
B. B.	Eczema............	11½ mos.	6,510	9.9	58.0	40.9	473	815	126	62	505	No reaction
		12 mos.	6,420	10.5	60.9	38.0+	494	811	126	57	462	Temp. 38 C., otherwise negative
B. L.	Hydrocephalus....	7 mos.	4,650	10.9	62.8	36.2	339	538	116	:	...	13 minutes late; no reaction
		7½ mos.	4,710	11.0	62.4	36.8	363	581	123	:	...	No reaction
		8 mos.	5,000	10.6	63.6	35.9	364	572	114	:	...	Loss 50 gm., O.K.
B. W.	Feeding case......	6 mos.	4,170	10.2	66.0	33.8	309	468	112	52	243	No reaction
		6½ mos.	4,320	11.0	66.0+	32.2	339	509	117	55	279	No reaction
B. N. B.	Birth palsy.......	10 mos.	7,800	12.2	65.5	34.0	465	710	91	:	...	No reaction
		10¼ mos.	7,900	9.75	65.1	33.8	466	714	90.3	:	...	No reaction
		11 mos.	7,960	9.1	67.5	31.3	614	908	114	:	...	Temp. 38.4 C., otherwise O.K.
		11¼ mos.	8,180	10.9	68.7	30.3	617	900	110	:	...	Temp. 40 C., otherwise O.K.

TABLE 5.—OF THREE INFANTS WITH FAIRLY MARKED SECONDARY ANEMIA

Name	Diagnosis	Age	Weight, Gm.	Total Hemat., C.c.	Plasma, per Cent.	Red Cell, per Cent.	Plasma Volume, C.c.	Blood Volume, C.c.	Blood per Kg., C.c.	Hb., per Cent.	Pigment Volume	Reaction
B. K.	Premature........	12 mos.	6,420	11.0	75.0	24.0	378	504	78.5	...	...	No reaction
		12¾ mos.	6,520	10.6	77.0	22.7	373	485	74.5	25	121	Temp. 39.2 C., loss 70 gm.
		12½ mos.	6,780	9.5	79.5	20.0	418	525	77.5	25	131	Temp. 38.2 C., otherwise O.K.
B. F.	Premature........	5½ mos.	3,080	10.9	72.0	27.0	216	300	97.5	52	156	Temp. 38.6 C.
		5¾ mos.	3,210	9.6	76.5	22.9	225	294	92.0	52	153	None
		6 mos.	3,280	10.2	80.2	18.6	230	288	87.5	:	...	Refused feedings for 2 days
B. C.	Premature........	7½ mos.	3,550	11.9	73.1	26.0	233	318	89.9	45	143	Temp. 39.6 C.
		8¼ mos.	3,830	10.5	80.5	19.0	295	366	95.6	25	91.5	None; loss 60 gm.
		8½ mos.	3,860	10.55	82.5	17.0	351	425	110.0	20	85	Temp. 38.2 C. (otitis media)
		9 mos.	4,760	10.1	69.2	29.0	390	560	118.0	37	207	No reaction

or produce these variations. Some points are, however, interesting enough to be emphasized. In B. K. (Table 5) the blood volume is very low, from 74.5 to 78.5 c.c. per kilogram of body weight. He was a typical fat, water-logged baby of the type so often seen which has been fed on a high carbohydrate diet. His plasma per cent., from 75 to 79.5, was very high in comparison with the other normal children of his age as B. N. B. who had a blood plasma of from 65 to 68.7 per cent. and a blood volume of from 90.3 to 114 c.c. per kilogram. B. F. and B. C. show the blood volume of quite marked secondary anemia so often found in premature infants. B. C., in addition, has as marked a clinical type of rickets as is often seen. Their plasma per cent. was also very high (from 69.2 to 82.5) and their red cell per cent. from 17 to 29, very low, as might be expected. In another case of severe anemia in an older child, not here reported, the plasma volume ran up to 85+ per cent. and the red cell percentage was 14.

While making these studies on blood volume, we have been struck by the practically uniform appearance of bile pigment in the serum of the new-born infants. The serum when pipetted off has a yellowish color. We have had several samples tested for bile pigment and in all bile pigments have been demonstrated.

Bang [10] found bile pigment in the blood obtained from the umbilical cord. He concludes that icterus in the new-born is a physiologic condition and the amount of pigment shows a constant increase in the blood after the first few days; he considers it only a question of degree between the new-born with or without icterus neonatorum. Our findings would corroborate Bang's findings. In many of our cases icterus, in so far as we were able to observe it, never appeared.

We are now making a more careful analytical study of this condition and hope to report on it in the near future. This undoubtedly has a distinct bearing on the appearance of certain of the hemorrhagic conditions of the new-born. In one of our babies which showed icterus almost from birth (it was observed when 4 hours old) bile pigment was present in very large amounts as shown by the marked discoloration of the serum when we made our blood volume determinations at 10 hours of age.

10. Bang, F.: Jaundice of the Newly-Born, Hospitalstidende **8**:637 (June) 1915.

11. Hooper and Whipple: Am. J. Physiol. **40**:332, 349 (April) 1916.

EFFECT OF INJECTION OF NONSPECIFIC PROTEIN ON DIPHTHERIA VIRULENCE TESTS IN GUINEA-PIGS *

HENRIETTA A. CALHOUN, M.D.

Assistant Professor of Pathology and Bacteriology, State University of Iowa

IOWA CITY

CONTROVERSY CONCERNING THE VALUE OF HORSE SERUM

Bingel,[1] noting that toxic cases of diphtheria, in which the most marked effect might be anticipated from antitoxin treatment, react only slightly, questioned the possibility of nonspecific reaction due to a foreign serum. He treated alternating cases of diphtheria entering the hospital with normal horse serum and with antitoxin. He was unable to see any appreciable difference between the 471 horse serum treated cases and the 466 antitoxin treated cases. The bacilli disappeared after four weeks in 89.6 per cent. of the antitoxin treated cases and in 94.6 per cent. of the horse serum cases. He concluded that the success of the serum therapy in diphtheria was dependent on the larger amount of horse serum used with the larger doses of antitoxin. Perhaps Bingel's results with horse serum may be due to the fact that only 45.7 per cent. of his antitoxin treated cases received antitoxin on the third day, or earlier, while 61.1 per cent. of the horse serum treated cases received injections on the third day or earlier.

This communication of Bingel's led to the most violent criticism. Johannovics [2] considered with astonishment this "bolt from a clear sky," and marshalled statistics to prove that antitoxin was specific, although it has long been granted that it was not so efficient in toxic forms of diphtheria where generalized poisoning occurred before specific serum therapy was started. He questioned the ethics of experimenting on

1. Bingel, A.: Ueber Behandlung der Diphtherie mit gewöhnlichem Pferdeserum, Deutsch. Arch. f. klin. Med. **125**:284, 1918.

2. Johannovics, G.: Zur Behandlung der Diphtherie mit gewöhnlichem Pferdeserum, Wien. klin. Wchnschr. **32**:220 (Feb. 27) 1919.

patients, and quoted Groer's [3] conclusions that antitoxin-free horse serum may not limit the specific diphtheria toxin effect in man. Then he figured that in 200 cases treated with normal horse serum on the first day, Bingel would have lost seven cases that could have been saved by the use of antitoxin.

Feer [4] tested the value of normal horse serum in mild cases only, giving 13 c.c. of horse serum intramuscularly. These mild cases took longer to clear up than the more severe antitoxin treated cases, and in six cases it became necessary to give antitoxin in addition to horse serum. In no case with horse serum treatment was there the favorable red line of demarkation on the mucous membranes, which was frequently observed with antitoxin treated cases.

Friedberger,[5] using diphtheria bacilli instead of diphtheria toxin, gave guinea-pigs about five times the fatal dose of a known culture of B. diphtheriae isolated from a fatal case. He then attempted to cure them with horse serum, using an intravenous injection of 0.5 c.c. or less of normal horse serum. He found that animals with an overdose of horse serum died earlier than animals with a small dose or than animals without any horse serum. His series was small, the table showing only twenty animals for two strengths of antitoxin, two sets of horse serum, and two control pigs without either horse serum or antitoxin treatment. He concluded that in guinea-pigs highly virulent diphtheria infections were not affected by normal horse serum in large doses, while antitoxin had a prompt effect.

Kolle and Schloszberger,[6] experimenting on animals, decided that normal horse serum therapeutically did not act as antitoxic serum in guinea-pigs. They used diphtheria toxin and attempted to cure 196 pigs with normal horse serum. Of these 48 died the first day after the toxin injection before any treatment was given, and of 53 treated pigs only 2 lived, as compared to the 95 pigs with antitoxin treatment, of which 51 recovered and 44 died. They gave three times the fatal dose of toxin, and in both horse serum and antitoxin treated pigs there were extensive areas of necrosis. They found that with both living diphtheria organisms and diphtheria toxin there was a slight curative action in large doses of horse serum when the time elapsing

3. Groer: Zur Frage der Bedeutung aspizifisher ergotroper Wirkungen des Serums bei der Heilserum-therapie der Diphtherie, Ztschr. f. d. ges. exp. Med. 7:171, 1918.

4. Feer, E.: Zur Behandlung der Diphtherie mit gewöhnlichem Pferdeserum, München. med. Wchnschr. 66:343 (March 28) 1919.

5. Friedberger, E.: Hat das normale Pferdeserum einen Einfluss auf die experimentelle Infection des Meerschweinchens mit Diphtherie-bazillen, Berl. klin. Wchnschr. 56:151 (Feb. 17) 1919.

6. Kolle, W., and Schloszberger, H.: Zur Frage der Heilwirkung des Diphtherieserums, Med. Klin. 15:1, 83, 1919.

before the injection was not more than from four to six hours postinfection.

This outlines the controversy which led to the experiments reported in this paper. There is no question at all concerning the specificity of antitoxin, in large doses, in diphtheria, but what is the effect of foreign protein injection on the results of the virulence tests for diphtheria in guinea-pigs? Can it be substituted in an emergency for antitoxin?

METHOD USED FOR VIRULENCE TESTS

At the time when this work was started our laboratory was engaged in an intensive study of a large series of diphtheria strains obtained from different sources, and my work is testing the virulence of the strains. We use the intracutaneous or intradermal test outlined by Zingher and Soletsky.[7] We modify the method slightly so that our standard method consists in shaving the abdomen of a guinea-pig, making room for 6 or 8 intracutaneous tests. Two pigs constitute the routine series; one, the test pig, receives the intradermal injection of 0.15 c.c. of a suspension of a twenty-four hour growth on a Loeffler's blood serum tube in 15 c.c. of sterile 0.9 per cent. sodium chlorid solution. The other pig, the control pig, receives the same intradermal injections immediately following the intracardial injection of 250 units of diphtheria antitoxin which has a horse serum volume of from 0.25 to 0.50 c.c. The strains of *B. diphtheriae* are in pure culture. Shumway[8] has determined that a twenty-four hour growth on Loeffler's blood serum suspended in sterile 0.9 per cent. sodium chlorid solution gives more uniform results than a forty-eight hour bouillon culture. I have also determined that an intradermal injection of 0.15 c.c. gives reactions which are more easily read than an injection of 0.25 c.c., where pressure necrosis may become a complicating factor.

The intradermal test gives a reaction that is accurate. The circumscribed necrosis may be measured in size, in rate of development and in time of duration. If nonspecific protein therapy has an effect on diphtheria virulence we have here an easy method for determining that effect.

NONSPECIFIC PROTEINS USED

Two nonspecific proteins are in common therapeutic use for man; one, typhoid vaccine; the other, normal horse serum. Consequently, these are selected for the tests and checked, finally, with a single eggwhite series. The dosage is purposely made large; the typhoid vaccine

7. Zingher, A., and Soletsky, D.: An Economical Intracutaneous Method for Testing the Virulence of Diphtheria, J. Infect. Dis. **17**:454, 1915.

8. Shumway, V.: Unpublished Thesis for M.S. Degree, 1919, State University of Iowa Library, Iowa City.

is the ordinary commercial vaccine standardized so that 1 c.c. contains one billion dead typhoid organisms. The horse serum is obtained in 20 c.c. vials, and all the material used came from one lot, No. 29554-9892 F, with an expiration date of Oct. 22, 1920. Concerning this E. Lilly & Sons state in a letter dated July 14, 1920: "The horses delivering this serum have never been subjected to any immunizing processes," and, "we have very accurate records on all horses used for the production of normal horse serum." The guinea-pigs are standard sized pigs all closely approximating 250 gm. in weight, which have never been used for any laboratory tests.

THE METHOD OF INJECTING FOREIGN PROTEIN AND ANTITOXIN

For three years our laboratory has used the intracardial method for obtaining blood from rabbits and guinea-pigs and for the injection of antitoxin in virulence tests. The mortality is very low in the hands of one with a little experience, no anesthetic is required, and the method is more rapid and shows fewer complications than occur with the use of the jugular vein of the guinea-pig for intravenous injection. Among more than 150 pigs receiving intracardial injections there were two deaths, both due to penetration of the auricle instead of the ventricle, with a resultant hemorrhage into the pericardium. There are no cases of fatal embolism.

My method is to tie the pig on an animal board, feel for the apex beat with the most sensitive finger tip, just to the left of the sternum. This is usually the intercostal space on a line with the axilla. With a sterile needle enter this space, going almost vertically down. Sometimes the sense of touch tells one when the ventricle is entered, but the safest guide is the appearance of blood in the syringe on slight withdrawal of the piston. The volume of the foreign protein injected is 0.25 c.c. volume of typhoid vaccine and antitoxin, from 0.5 to 1 c.c. volume of horse serum and of egg white. This is injected rapidly to avoid any chance of the needle slipping from the heart cavity.

EFFECT OF THE INTRACARDIAL INJECTION OF TYPHOID VACCINE ON THE INTRACUTANEOUS TEST

Table 1 shows the effect of an intracardial injection of 250 million dead typhoid organisms immediately preceding the intracutaneous injection of 0.15 c.c. of a suspension of a twenty-four hour growth on Loeffler's blood serum in 15 c.c. of sterile isotonic salt solution.

This shows clearly that the intracardial injection of typhoid vaccine followed immediately by the intradermal injection of cultures of *B. diphtheriae* increases the sensitiveness of the virulence test. The necrosis occurs, as a rule, earlier, the reaction is more marked, usually larger

TABLE 1.—Effect of Intracardial Injection of 250 Million Dead Typhoid Bacilli Immediately Preceding the Injection of B. Diphtheriae Cultures Intracutaneously, Compared with Test Pigs and Antitoxin Controls

	Number and Strain of B. diphtheriae	Antitoxin Control Pig	Test Pig				Typhoid Vaccine Pig			
			First Reaction Noted	Necrosis	Lesion Cleared	Notes	First Reaction Noted	Necrosis	Lesion Cleared	Notes
1	2*	—	12 hours	5th day	12 days	....	12 hours	2d day marked	12 days	More rapid and marked
2	5*	—	36 hours	36 hours	8 days	....	33 hours	36 hours	13 days	Long duration
3	8*	—	18 hours	48 hours	Killed in 48 hours	....	18 hours	3d day	Died in 72 hours	
4	12*	—	24 hours	—	Died in 60 hours	....	24 hours	—	Died in 48 hours	Early death
5	15*	—	16 hours	36 hours	23 days	....	16 hours	4th day	31 days	Long duration
6	16	—	16 hours	4th day	4 days	Negative test	16 hours	24 hours	15 days	Positive
7	17	—	21 hours	—	8 days	....	18 hours	—	Died in 48 hours	Early death
8	21	—	16 hours	4th day	23 days	....	16 hours	38 hours	32 days	Rapid necrosis and long duration
9	25	—	38 hours	62 hours	11 days	....	36 hours	62 hours	14 days	Long duration
10	26	—	12 hours	—	7 days	Negative test	12 hours	48 hours	7 days	Positive
11	27	—	16 hours	4th day	13 days	....	16 hours	48 hours marked	14 days	More rapid and marked reaction
12	30†	—	—	—	—	Negative test	—	marked	Paralysis lasting 4 days	Negative test
13	31‡	—	16 hours	4th day	10 days	....	16 hours	4th day	20 days	Long duration
14	32	—	3 days	5th day	7 days	....	12 hours	48 hours	12 days	More rapid and longer duration
15	34	—	18 hours	—?	Killed on 3d day	Negative test	36 hours	4th day	Died on 4th day	Positive
16	36	—	12 hours	5th day	12 days	....	12 hours	2d day	12 days	More rapid
17	38	—	—	—	Killed on 3d day	Negative test	18 hours	3d day	Died on 4th day	Positive
18	39	—	—	—	Killed on 3d day	Negative test	18 hours	3d day	Died on 4th day	Positive
19	122	—	36 hours	5th day	13 days	....	36 hours	36 hours (25 mm.)		More rapid
20	140	—	60 hours	60 hours (8 mm.)	12 days	....	60 hours	60 hours	Not cleared in 28 days	Larger and longer duration
21	144	—	—	—	—	Negative test	60 hours	5th day (10 mm.)	12 days	Positive
22	145	—	36 hours	36 hours (5 mm.)	12 days	....	60 hours	3d day (10 mm.)	14 days	Larger and longer duration
23	146	—	24 hours	4th day	—	....	36 hours	36 hours	—	
24	147	—	—	—	—	Negative test	36 hours	36 hours	—	
25	154	—	24 hours	36 hours	12 days	....	36 hours	36 hours	—	Positive test

* Virulent on subcutaneous test.   † Toxin producing strain from Parke Davis.   ‡ Park 8.
Twenty-five different strains tested on 54 pigs. All strains tested were morphologically granular types which gave the sugar fermentation tests of true diphtheria.

in size and clears more slowly than the corresponding area in test pigs. In eight strains giving a negative intracutaneous test on the ordinary test pig, the reaction was definitely positive on the nonspecific protein pig receiving typhoid vaccine. The first explanation that suggests itself is that the diphtheria organism is being introduced during the leukopenia stage, when there is a lowered resistance and an increased sensibility so that varying the time of the typhoid injection might alter the result. But intracardial injections made as long as forty-eight hours preceding the intradermal tests do not change the reaction. The difference between the severity of the reactions on the typhoid pigs, the test pigs, and the control pigs is so marked that it is easy to pick out the different series without reference to the card records.

EFFECT OF THE INTRACARDIAL INJECTION OF HORSE SERUM ON THE INTRACUTANEOUS TEST

After testing the virulence of forty different strains with typhoid vaccine, and establishing the increase in the severity and the prolongation of the time of the reaction, horse serum is substituted as the nonspecific protein, 1 c.c. being injected into the heart immediately preceding the intradermal inoculation. The first twelve strains tested showed no reaction at all on the horse serum pigs, not even the hyperemia which is often seen on the antitoxin pigs during the first twelve hours. I was afraid the attendant might have confused the syringes, handing me an antitoxin syringe instead of one containing horse serum, hence these twelve tests were not included in the series, and they were repeated again. The results of the second test are the same as the first. Fifty different strains of *B. diphtheria* are tested. Twenty-five of these on a series of forty-two pigs are reported in Table 2. All these strains of *B. diphtheriae* are granular types giving the fermentation tests of true diphtheria organisms.

This series shows six test pigs with positive intracutaneous tests while the corresponding horse serum pigs show no reaction. Table 2 is also of interest because of the large number of typical diphtheria strains that are avirulent on the initial tests. In only one instance is there a positive reaction on the horse serum pig with a negative reaction on the test pig.

EFFECT OF TYPHOID VACCINE AND HORSE SERUM ON TESTS WITH DIPHTHERIA AND DIPHTHEROID ORGANISMS

The third series (Table 3) consists of pure cultures of virulent and nonvirulent diphtheria organisms and virulent and nonvirulent diphtheroid organisms. Each test includes four pigs in the series; a test pig, a control pig with antitoxin, a pig with typhoid vaccine, and a pig with horse serum.

TABLE 2.—Effect of Intracardial Injection of 1 c.c. Normal Horse Serum Immediately Preceding the Injection of B. Diphtheriae Intracutaneously, Compared with Test Pigs and Antitoxin Controls

Number and Strain of B. diphtheriae		Antitoxin Control Pig	Test Pig				Horse Serum Pig			
No.	Strain		First Reaction Noted	Necrosis	Lesion Cleared	Notes	First Reaction Noted	Necrosis	Lesion Cleared	Notes
51	40*	—	24 hours	—?	Died in 48 hours	....	72 hours	3d day	4 days	
52	44	—	24 hours	—?	Died in 48 hours	....	—	—	—	No reaction
53	45	—	14 hours	—?	Died in 48 hours	....	—	—	—	No reaction
54	50	—	14 hours	36 hours	Killed in 48 hours		—	—	—	No reaction
55	52	—	14 hours	—	Killed in 48 hours	Negative	—	—	—	No reaction
56	53	—	14 hours	—	—	Negative	—	—	—	No reaction
57	55	—	—	—	—	Negative	16 hours	40 hours	13 days	No reaction; Slower development
58	56	—	16 hours	16 hours	Died in 40 hours	Strongly positive	16 hours	5 days	9 days	Slow development of necrosis
59	57	—	16 hours	16 hours	Died in 36 hours	Very virulent	16 hours	40 hours	13 days	Slow development
60	61	—	16 hours	16 hours	....	Very virulent Sub. q.	40 hours	5 days	9 days	
61	68*	—	—	—	Died in 96 hours	Negative	16 hours	5 days	19 days	
62	80	—	—	—	—	Negative	16 hours	5 days	19 days	Positive
63	65	—	16 hours	40 hours	Pig killed		16 hours	72 hours	12 days	Slower development
64	88	—	16 hours	4th day	Pig died		16 hours	72 hours	9 days	No reaction
65	89	—	—	—	4 days	Negative	—	—	—	No reaction
66	97	—	72 hours	72 hours	Pig killed	....	—	—	—	No reaction
67	102	—	48 hours	72 hours	Died in 72 hours	....	24 hours	72 hours	23 days	
68	107	—	24 hours	48 hours	Died in 72 hours	Very virulent	24 hours	72 hours	6 days	
69	109	—	48 hours	48 hours	Died in 72 hours	Very virulent	24 hours	72 hours	23 days	
70	111	—	24 hours	72 hours	Died in 72 hours		24 hours	72 hours		
71	114	—	24 hours	48 hours	Pig killed	....	24 hours		4 days	No reaction
72	115	—	—	—		Negative	—	—	—	No reaction
73	140	—	—	—		Negative	—	—	—	No reaction
74	142	—	60 hours	72 hours	12 days	....	—	—	—	No reaction
75	145	—	36 hours	36 hours	12 days	....	—	—	—	

* Virulent on subcutaneous test.   Twenty-five different strains tested on 42 pigs.

The findings, in general, are those of the first series—a more severe reaction which lasts longer with the typhoid pig showing a lowered resistance and a less marked reaction with the horse serum pig showing some protective action on the part of horse serum.   Table 3 is also of interest because it shows a virulent diphtheroid, strain 82, in which there is a positive reaction on the antitoxin control pig as well as the test and nonspecific protein pigs.   There is also another strain, No. 143, a diphtheroid by morphology and fermentation tests which on virulence tests acts as a true virulent diphtheria organism.

PROTECTIVE AND THERAPEUTIC EFFECT OF TYPHOID VACCINE AND HORSE SERUM ON SUBCUTANEOUS INJECTION OF DIPHTHERIA CULTURES

If there is a protective action in horse serum and a lowered resistance with typhoid vaccine it should show on the subcutaneous test with a known virulent strain of B. diphtheria.   Strain 15, a granular type, fermenting dextrose and dextrin, which was isolated from a case of mild diphtheria Jan. 8, 1920, kills guinea-pigs in from thirty to seventy-two hours, when 1 c.c. suspension of a twenty-four hour growth is injected subcutaneously.

The first series consists of thirty pigs.   These pigs are divided into groups of 2.   Forty-eight hours preceding the time set for the subcutaneous injection of B. diphtheriae, one group is given 250 million dead typhoid organisms intracardial and another group 1 c.c. of normal horse serum; this is repeated with successive groups at intervals corresponding to twenty-four hours, six hours, two hours, one hour and one-half hour, and immediately preceding the injection of cultures of strain 15.   Thirty pigs can be given subcutaneous injections within a time interval of twenty minutes.   The suspension is made by pooling the twenty-four hour growth on thirty-five Loeffler tubes in 35 c.c. of sterile 0.9 per cent. sodium chlorid solution.   One c.c. of this pooled suspension is injected into each pig.   The test pigs received this suspension without other treatment.   All pigs that die are autopsied.   A subcutaneous virulence test is read as positive if a 1 c.c. suspension causes the death of a standard sized guinea pig in 120 hours.

The second series consists of thirty-two pigs all of which are given 1 c.c. of a pooled suspension of a twenty-four hour growth on thirty-five Loeffler tubes in 35 c.c. of sterile salt solution subcutaneously.   The total time for all the subcutaneous injections is under twenty minutes. Immediately following the subcutaneous injection, one group of two pigs is given 250 million dead typhoid organisms, one group of two pigs (the test pigs) receive no other treatment and one group of two pigs is given 1 c.c. of normal horse serum intracardially.   Typhoid and

Series No.	Culture No.	Control Pig	Test Pig			Typhoid Vaccine Pig			Horse Serum Pig		
			First + Reading	Necrosis	Lesion Cleared	First + Reading	Necrosis	Lesion Cleared	First + Reading	Necrosis	Lesion Cleared
100	48§	—	7 hours	3d day	Pig killed 3d day	18 hours	3d day	Pig died on 4th day	3d day	3d day	4 days
101	140§	—	60 hours	60 hours (3 mm.)	12 days	60 hours	60 hours (24 mm.)	Present in 28 days	60 hours	60 hours (4 mm.)	5 days
102	141§	—	—	—	—	Hyperemia 18 hours	—	24 hours	—	—	—
103	142§	—	60 hours	72 hours (2 mm.)	12 days	60 hours	5 days (5 mm.)	Present in 14 days	—	—	—
104	144§	—	—	36 hours (3 mm.)	12 days	60 hours	5 days	12 days	—	—	—
105	145	—	36 hours	3d day (4 mm.)	12 days	60 hours	3 days (10 mm.)	Present in 14 days	—	—	—
106	143‖	—	72 hours			—	—	14 days	—	—	—
107	139†	—	—	—	—	—	—	—	—	—	—
108	134†	—	—	—	—	—	—	—	—	—	—
109	131*	—	—	—	—	—	—	—	—	—	—
110	82#	+	16 hours	72 hours	Pig died on 4th day	16 hours	40 hours	9 days	16 hours	40 hours	9 days

horse serum injections are repeated at one-half, one, two, nineteen and twenty-four hours postinjection for both of the nonspecific proteins and three, four and six hours postinjection for the normal horse serum pigs.

Each series is controlled by two pigs receiving 250 units of antitoxin, and the 1 c.c. suspension of virulent diphtheria organisms subcutaneously. These pigs are not included in the charts. All these control pigs are living on the seventh day.

It is strikingly shown that all the pigs receiving an intracardial injection of typhoid vaccine and a virulent diphtheria organism subcutaneosuly die in less than 120 hours, regardless of whether the nonspecific protein is injected forty-eight hours before or twenty-four
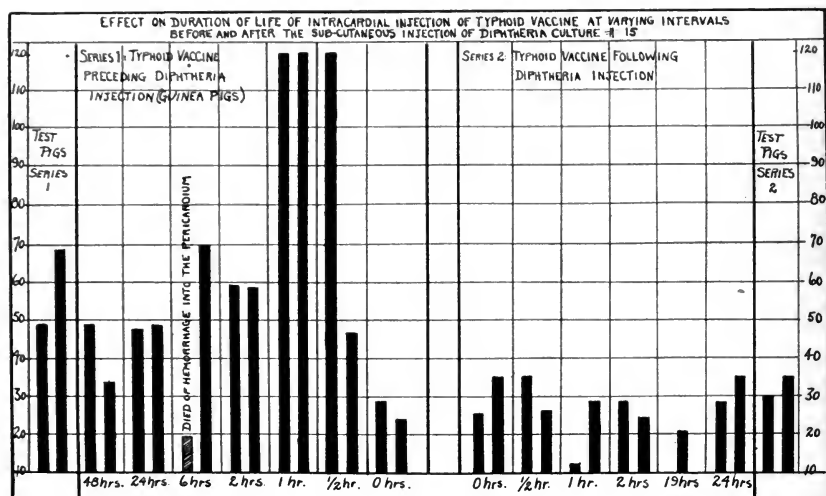
Fig. 1.—Black columns indicate dead guinea-pigs, the height of the column corresponding to the duration of life in hours.

hours afterward. The test pigs and twenty-two of the typhoid pigs are dead in less than seventy hours, while three pigs live 120 hours. There is evidently no protection given by typhoid vaccine against diphtheria inoculations in guinea-pigs. Typhoid vaccine has no therapeutic value in the treatment of diphtheria infections in guinea-pigs.

Normal horse serum, on the contrary, shows a very definite protective value given from forty-eight hours to immediately preceding the subcutaneous inoculation with B. diphtheriae, No. 15. Untreated pigs die in less than seventy hours, while twelve out of fourteen pigs given 1 c.c. of horse serum are living at the end of five days. Of the two that are dead, one died in eighteen hours following the intracardial injection due to hemorrhage into the pericardium. The other died in

fifty hours postinoculation, showing typical hemorrhage into the supra-renals, congestion of the lungs and fluid in both pleural and peritoneal cavities. Following the subcutaneous inoculations of guinea-pigs with virulent diphtheria organisms, 1 c.c. of horse serum will protect, if it is given any time up to five hours postinoculation. After six hours it has no effect, the pigs dying in the same period of time (under thirty-five hours) as the test pigs of this series.

Horse serum protection is in no way comparable in its protective value to the action of large doses of antitoxin. Cruveilhier [9] could rescue guinea-pigs sixteen hours after injection with a virulent diphtheria strain by the intravenous injection of antitoxin where untreated animals died in from thirty-six to forty-eight hours.
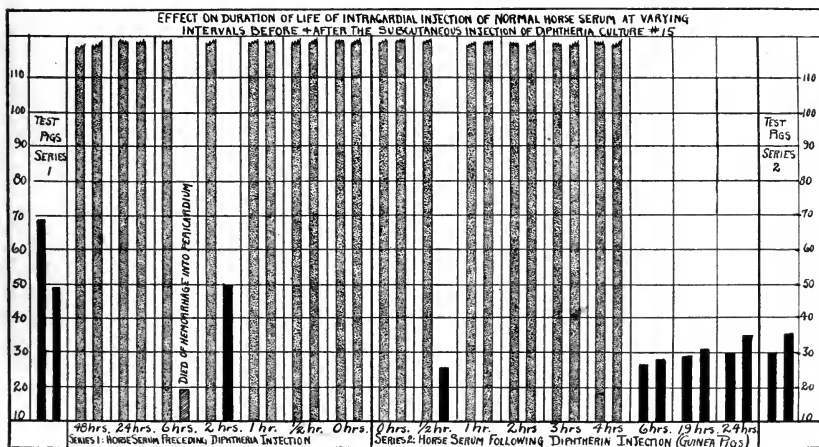
Fig. 2.—Black columns indicate dead guinea-pigs, the height of the column corresponding to the duration of the life in hours. Stippled columns indicate pigs living at the end of the period of observation.

Kolle and Schloszberger,[6] using diphtheria toxin, find that there is a certain death retarding effect but that it is slight, and it decreases with the time interval. With very small doses of antitoxin, the pigs died of necrosis after from twenty to twenty-five days. Of their 216 antitoxin treated pigs, 70 per cent. lived, while of 137 horse serum treated pigs, 80 per cent. died. They speak of the extensive necrosis which occurs with small doses of antitoxin. This necrosis occurs constantly in the horse serum tested pigs and is so extensive that the pigs are killed in from seven to fourteen days. Three pigs from the series illustrated in the charts are shown in Figure 3.

9. Cruveilhier, L.: De la Valeur Thérapeutique des injections de Serum dans la diphtherie suivant les doses et la voie de penetration, Ann. de l'Inst. Pasteur **18**:41, 1904.

The necrosis extends to the deeper muscle layers in the abdominal wall. In a few pigs showing a slighter degree of necrosis, the ulcer heals with smooth scar tissue, and no hair develops on the area of the scar.

FACTORS ENTERING INTO THE PROTECTIVE ACTION OF HORSE SERUM

What are the factors entering into this protective action of horse serum? Hektoen and Curtis [10] find that the injection of 1 c.c. of 10 per cent. suspension of rat blood per kilo of body weight in dogs produces specific opsonins and agglutinins which run parallel and only
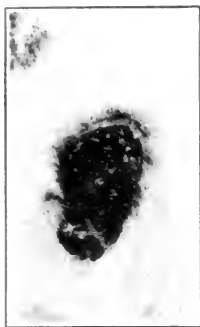
Fig. 3 a   Fig. 3 b   Fig. 3 c

Fig. 3.—Necrosis in horse serum treated pigs. Photographed by Johannes Andersen.

small amounts of lysin and precipitins are produced. Herrmann [11] believes that the intravenous injection of foreign protein serves as a stimulus for the liberation of specific antibodies in animals in which the previously injected antigen (streptococcus) is unable to cause such liberation. Jobling and Petersen [12] show marked change in the ferments and antiferments in the blood in protein shock, the protease and ereptase increase probably aiding in detoxication. They think toxins are hydrolyzed by ferments to lower nontoxic forms, so that a temporary improvement of a few days' duration may be observed, but that bacteria themselves are unaffected by these ferments. This latter may

10. Hektoen and Curtis: The Effect on Antibody production of the Removal of Various Organs, J. Infect. Dis. **17**:409, 1913.

11. Herrmann, S.: Liberation of Antibodies on the Injection of Foreign Proteins, J. Infect. Dis. **23**:457, 1918.

12. Jobling, J. W., and Petersen, W.: Bacteriotherapy in Typhoid Fever, J. A. M. A. **65**:515, 1915.

perhaps explain the question of the protection with horse serum injections, for the dose of 1 c.c. intracardially of horse serum is an enormous dose for a 250 gm. guinea-pig—roughly speaking it increases the guinea-pig's blood fluids by one-eighth of the total blood volume, and the simple injection of that quantity of antibodies may give protection until the body is able to mobilize its own protective forces. Or, perhaps, protection may be the result of nonspecific protein reactions. This, at first glance, seems untenable since typhoid vaccine gives no protection in guinea-pigs. But what constitutes the nonspecific protein reaction? The phenomenon of protein shock is characterized by the syndrome of chills, fever and changes in the blood picture during the first forty-eight to seventy-two hours after intravenous injection of a foreign protein.[13]

In guinea-pigs it is difficult to measure the temperature response to a specific agent since fright and excitement without any other factors will cause change of as much as 3 degrees in the rectal temperature of a guinea-pig, and an animal unaccustomed to handling will frequently shake as though with a chill when it is handled. No definite physical symptoms are noted after intracardial injection of 0.25 c.c. of typhoid vaccine. Increasing the volume up to 1 c.c. by diluting with normal salt also has no effect on the physical reaction. The horse serum pigs, however, exhibit some respiratory distress immediately following the injection of 1 c.c. To check the existence of protein shock blood counts are made following the method used by Cowie and Calhoun[15] in studying the effect of nonspecific protein therapy in arthritis. Leukocyte counts are made preceding the injection of the typhoid vaccine and horse serum, every half hour postinjection for two hours, and then every hour until the count returns to normal. The blood is taken from the ear of the guinea-pig, diluted with 1 per cent. acetic acid in the white pipet and counted in a Levi chamber. Both pipet and counting chamber have been tested and certified by the U. S. Bureau of Standards. The normal picture of a foreign protein reaction is a leukopenia followed by a leukocytosis chiefly due to an increase in the polymorphonuclear group. In man there are two types of the reaction; one with a prompt rise from the leukopenia, followed by a

---

* Barach[14] criticizes the statement made by Cowie and Calhoun,[15] that the protein shock or nonspecific protein reaction is not anaphylactic in its nature. We hold that there is a clear distinction between the primary protein shock reaction, and the secondary anaphylactic response to a previous sensitization— anaphylaxis meaning always a reaction to a preceding injection which is specific for the protein injected.

13. Borach[14] criticizes the statement made by Cowie and Calhoun,[15] that the

14. Barach, J. H.: Leukocytes in Anaphylaxis of Serum Sickness, J. Lab. & Clin. M. **5**:295 (Aug. 7) 1920.

15. Cowie and Calhoun: Nonspecific Therapy in Arthritis and Infections, Arch. Int. Med. **23**:60 (Jan.) 1919.

permanent return to normal in from nine to twelve hours; and the other, the type with a primary rise and fall which is followed in the course of from six to twenty-four hours by a secondary rise, sometimes to a higher point than the first—the pendulum type described by Miller and Lusk.[16]

ESTABLISHMENT OF NORMAL WHITE BLOOD COUNT IN GUINEA-PIGS

Eyre [17] gives the normal white count for a guinea-pig as 10,000 per c.mm. This is found to be subject to wide variation in different pigs, and in the same animal at different times of the day.

Counts made on three normal pigs at two hour intervals, seven counts in each series, show a range of from 6,200 to 14,300 leukocytes, with the peak count between 2 and 3 p. m. Counts made on twenty-four different pigs between 8 and 10 a. m. show a leukocyte range of from 6,400 to 21,500, distributed as follows:

TABLE 4.—LEUKOCYTE COUNT MADE BETWEEN 8 AND 10 A. M.

Number of Pigs	Leukocyte Range
1	21,500
13	10,500-15,000
6	9,500-10,500
3	8,000- 9,500
1	6,400

From these figures it seems that the normal range of the leukocyte count in healthy standard size guinea-pigs is from 8,000 to 15,000. Guinea-pigs showing an initial count falling outside this range were not used for the study of the blood reactions.

For purposes of facilitating comparison, the counts on individual pigs are reduced to the standard average of 10,000 for the initial count and the curves are calculated on the basis of percentage of increase or decrease from the true initial count. The individual normal range is between 8,000 and 15,000, the counts in normal pigs tending to remain in most cases above the 10,000 line rather than below it.

LEUKOCYTE COUNT AFTER INJECTION OF TYPHOID VACCINE
AND HORSE SERUM

The effect on the leukocyte count of the intracardial injection of 250 million dead typhoid bacilli on two guinea-pigs is shown in Figure 4, the counts extending over a period of twenty-eight hours with a final count in thirty-six hours. This shows the startling fact that in guinea-pigs, 250 million dead typhoid organisms do not give the typical blood picture of a foreign protein. For the first six to eight hours

16. Miller, J. L., and Lusk, F. B.: The Treatment of Arthritis by the Intravenous Injection of Foreign Proteins, J. A. M. A. **66**:1756 (June 3) 1916.

17. Eyre, J. W. H.: The Elements of Bacteriologic Technic, Ed. 2. Philadelphia, W. B. Saunders & Company, 1915, p. 374.

there is a tendency for the count to drop below the normal limits and a definite leukocytosis does not occur before from twenty-three to twenty-six hours postinjection. Its range is from 23,000 to 26,000 per c. mm. From this we must conclude that foreign proteins do not act as foreign proteins for all animals—either the guinea-pig does not have the ability to split the protein of the typhoid organism, or, on being split, typhoid protein does not liberate harmful or stimulative substances that are able to act on the spleen, bone marrow and lymphatic centers—the mesenchymal fundaments. That the action of non-
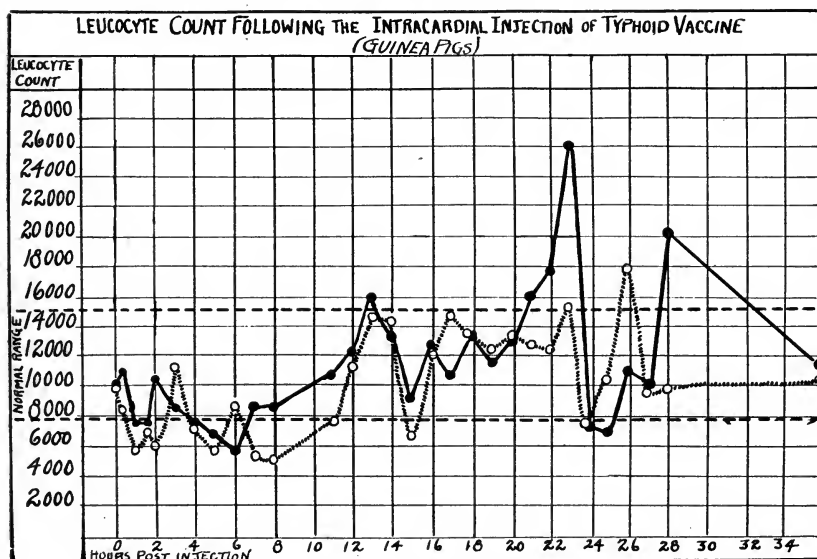
Fig. 4.—Individual counts on two guinea-pigs shown by solid and dotted lines.

specific proteins varies in different species of animals is also borne out by the fact that Cohen[18] finds that parenteral injection of egg white has no effect on the temperature of the dog, although the egg white is absorbed from the point of injection and is not excreted in the urine as egg white, but in the guinea-pig the injection of egg white produces the typical protein fever.

The leukocyte count following the intracardial injection of 1 c.c. of normal horse serum shows the typical foreign protein curve. The two pigs illustrated show the two types of curves, one the simple leukopenia and hyperleukocytosis and the other the leukopenia and a leukocytosis with a pendulum swing, the second rise being the highest, with a third rise in thirty-six hours. There is no doubt that here there is a definite foreign protein blood picture which seems to add evidence

18. Cohen, S. J.: Protein Fever: the Effect of Egg White Injection on the Dog, J. Lab. & Clin. M. **5**:285, 1920.

to the theory that the cellular elements play an essential part in the protective mechanism of the body. The increase in leukocytes appears even more marked when the volume dilution of one-eighteenth is recalled.

What is the relationship between the leukocyte change in diphtheria intoxications and the time interval beyond which the horse serum exerts no protective or therapeutic value? Figure 6 shows the counts made on two pigs which received a subcutaneous injection of a 1 c.c. suspension of a twenty-four hour growth on Loeffler's blood serum of *B. diphtheriae* strain 15.
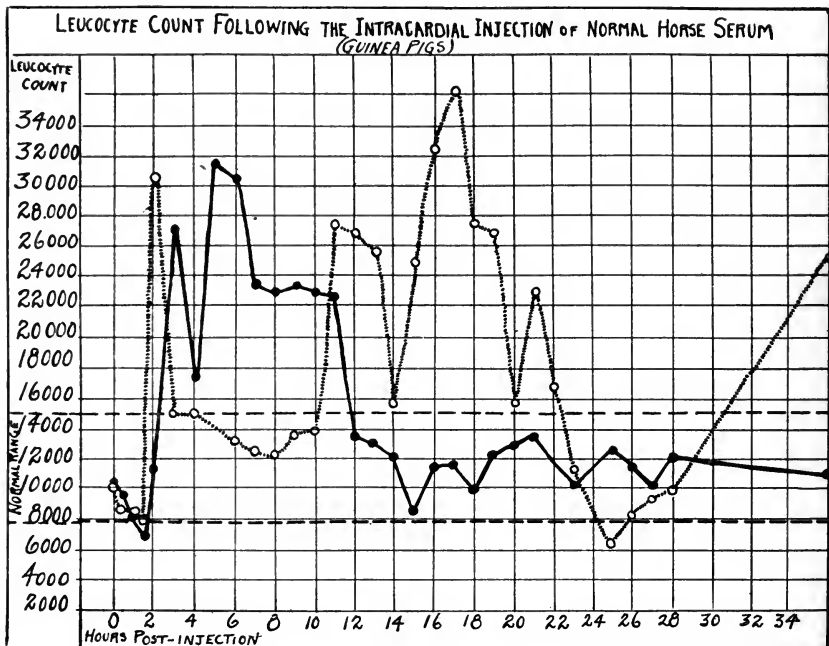
Fig. 5.—Individual counts on two guinea-pigs shown by solid and dotted lines.

There is a leukocytosis which reaches its first peak in from four to ten hours and is followed by a fall, with a second marked rise in twenty-two hours and a rapid fall preceding death. One pig shows a maximum leukocytosis of 68,000, the other a maximum of 30,000. With an injection of horse serum up to six hours postdiphtheria injection it may be noted that the leukopenia stage occurs with a rising count in the untreated pig and the first leukocyte rise in the horse serum pig with a falling leukocyte count in the diphtheria pig. However, it is impossible to get any definite correlation on counts following the simultaneous injection of the typhoid vaccine and the organism, the curves in different pigs showing wide variations.
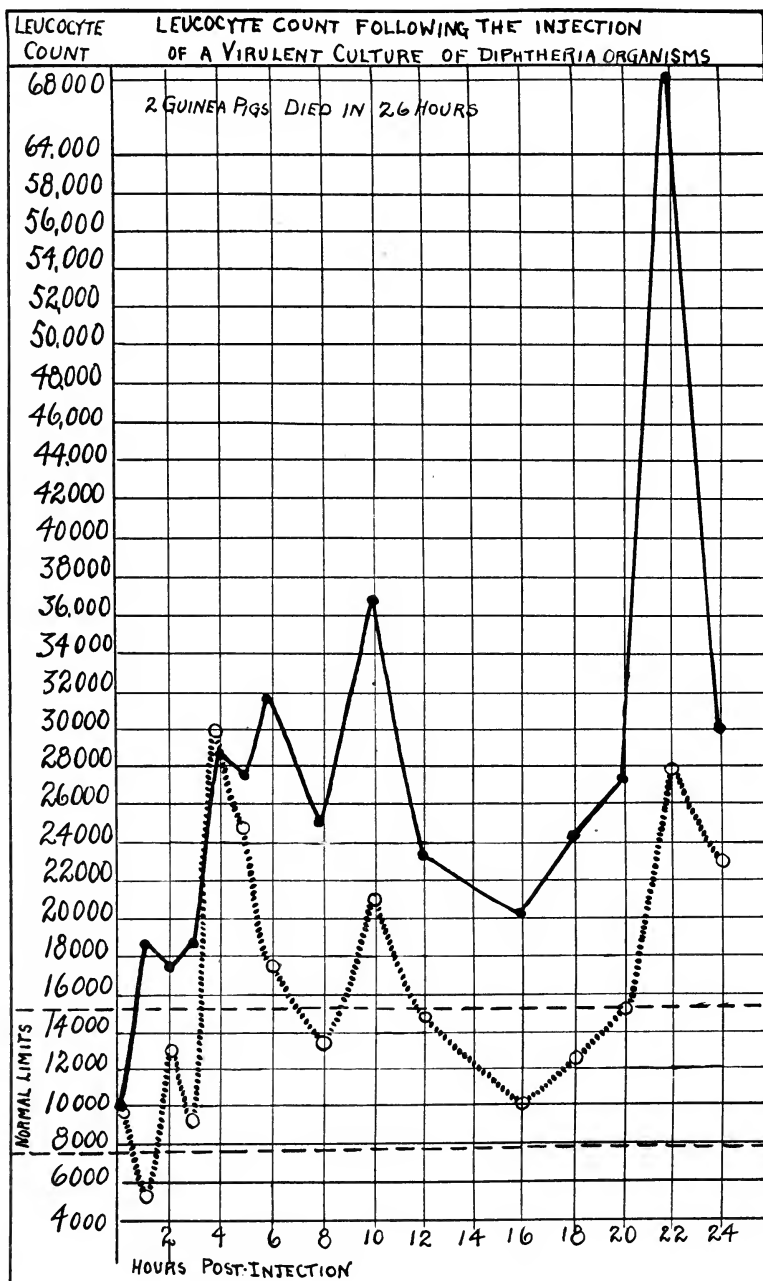
Fig. 6.—Individual counts on two guinea-pigs shown by solid and dotted lines.

Counts made on pigs receiving 0.25 c.c. of horse serum volume containing 250 units of antitoxin do not show any definite variations from the normal.

TESTS OF ANTITOXIN EQUIVALENT OF HORSE SERUM

Is there a possibility that horse serum may derive its protective action from its antitoxic content? Many horses produce low titers of antitoxin and many undoubtedly naturally produce serums with small amounts of antitoxin. Diphtheria toxin (Mulfords No. 837.5) was obtained. The L+ dose is 0.20 c.c. If 0.20 c.c. of the toxin will just kill a standard sized guinea-pig which has been given 1 unit of antitoxin in 5 days then it is possible to ascertain the antitoxin equivalent of the 1 c.c. horse serum used.

TABLE 5.—TEST FOR ANTITOXIN CONTENT OF HORSE SERUM

Number of Pigs	Amount of Toxin, C.c.	Amount of Horse Serum, C.c.	Results
2	0.20	0	Death in 18 hours
2	0.20	0.25	Death in 24 hours
2	0.20	0.35	Death in 100 to 120 hours
2	0.20	0.50	Living in 7 days
1	0.20	1.0	Living in 7 days
2	0.20	1 standard unit antitoxin	Death in 100 to 118 hours

This shows that there is less than one unit value of antitoxin in 0.33 c.c. horse serum used since the pigs with an L+ dose are not protected for five days, while 0.5 c.c. horse serum contains more than one unit value of antitoxin. Consequently, the antitoxin equivalent of 1 c.c. horse serum is between 2 and 3 standard units of antitoxin. Of course, this does not rule out the possibility that the antitoxin equivalent of horse serum may be due to some other antibodies, opsonins, agglutinins,[10] and ferments or antiferments as protease or ereptase [12] which may be present in the horse serum injected, in sufficient quantity to protect; or to antibodies which may be developed in the blood of the guinea-pig as a result of the foreign protein reaction to horse serum. This point cannot be settled by animal experimentation until we have a new method for testing antitoxin. Personally, I think the antibody is probably specific diphtheria antitoxin contained in the horse serum.

PROTECTIVE VALUE OF SMALL AMOUNTS OF ANTITOXIN

Can the small amount of antitoxin in 1 c.c. horse serum protect a 250 gm. guinea-pig for five days against a subcutaneous injection of a virulent strain of *B. diphtheriae*?

To determine this a series of twenty-five pigs are inoculated. Four are used as test pigs, and three of each set are given a varying amount of standard measurable units of antitoxin. This antitoxin is from the hygienic laboratory and was obtained through the kindness of Dr. McCoy. In doses of from 12 to 24 units it is necessary, because of the dilution, to inject the antitoxin subcutaneously. The remaining tests are all intracardial.

The diphtheria organism selected is strain 198, which kills test pigs in from eighteen to forty hours after the subcutaneous injection of 1 c.c. suspension of a twenty-four hour growth on Loeffler's tubes. The growth on thirty-five tubes is pooled in 35 c.c. of sterile isotonic salt solution, and each pig is given 1 c.c. of this suspension. One unit of antitoxin retards death, from one and one-half to six days; 3 units of antitoxin retard death from seven to eight days, and 6 units and
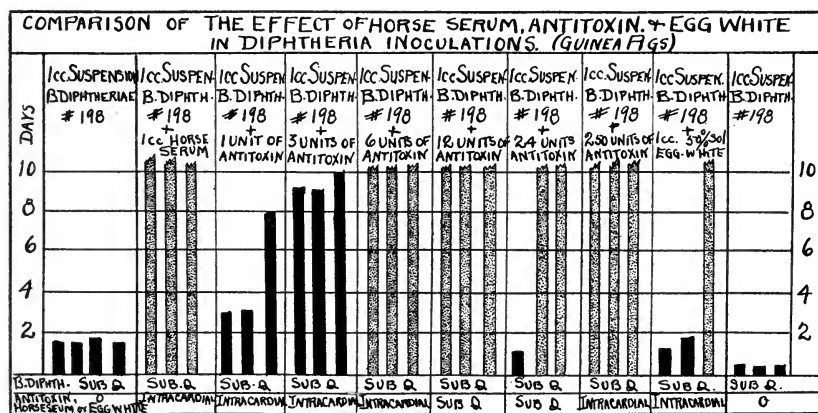
Fig. 7.—Black columns indicate dead guinea-pigs, the height of the column corresponding to the duration of life in hours. Stippled columns indicate pigs living at the end of the period of observation.

over (with one exception) protect against virulent diphtheria organisms. The most interesting fact is that, although 1 c.c. horse serum contains an antitoxin equivalent of less than three units, the smallest dosage of a standard antitoxin that will give the same protection is 6 units.

PROTECTIVE FACTORS IN HORSE SERUM

This seems to show that the big factor in horse serum protection against virulent diphtheria organisms in guinea-pigs is its antitoxin equivalent, and yet that this is not the only factor is shown by the fact that the equivalent amount of antitoxin does not give as efficient protection. Is this additional factor the nonspecific protein reaction?

The tests with typhoid vaccine do not give any clue to this because in a guinea-pig the dead typhoid bacilli do not give the protein response. To check this point a series of six pigs—three test pigs and three protein pigs—are used for tests with egg white, which gives a protein reaction in guinea-pigs. The dosage of egg white is 1 c.c. of a 50 per cent. solution of egg white in sterile salt solution, injected into the heart. The results are also shown in Chart 7. The egg white pigs lived from twenty-four hours to 14 + days longer than the corresponding test pigs. This means that there is a retardation of the time of death caused by the injection of egg white, which in one case out of three was equivalent to that produced by horse serum or by 6 units of antitoxin. The foreign protein reaction on the part of the guinea-pig following the injection of horse serum must be considered as a part of the protective power of the horse serum.

It must be concluded that the mechanism of this protective power is due: first, to an antibody, probably antitoxin in the horse serum; and second, to the calling forth of the protective forces in the guinea-pig, chiefly, I believe, in the form of cellular response to the foreign proteins in the horse serum that aids in the protection. Undoubtedly, the antitoxin factor is the most important because there is cellular response called forth by the subcutaneous inoculation with living diphtheria cultures, the leukocyte counts made at intervals on test pigs following the inoculation showing the pendulum type of curve. The diphtheria curves do not exactly coincide with the foreign protein curves in the time of development, but this may be due to the fact that the typhoid vaccine, egg white and horse serum are given intracardially in the form of protein, and the diphtheria organisms are given intracutaneously in the form of living protoplasm which may give no reaction until it is autolyzed.

The controversy over the question of the relative importance of the value of cellular response and of the soluble antibody production as a result of the injection of a foreign protein is still unsettled. However, I cannot help but feel that this adds corroborative evidence to the findings previously given by Cowie and Calhoun, that in arthritis the most marked and permanent improvement in protein treated cases occurs in those cases in which there is the most marked cellular response, a response that calls forth both the reserve and the unfinished blood cells and is evidenced by the appearance of myelocytes and nucleated red cells.

CONCLUSIONS

1. Typhoid vaccine, administered intracardially, increases the sensitiveness of the virulence tests both by the intradermal and the subcutaneous methods. With intradermal injection the reaction is earlier,

more marked and persists for a longer period of time, and the percentage of positives is larger than in ordinary test pigs.

2. Horse serum injected intracardially decreases and inhibits the intracutaneous test for virulent diphtheria organisms. In guinea-pigs injected with horse serum inoculations showing a positive reaction on intracutaneous tests the lesions are less marked and clear up more rapidly than in the corresponding test pigs.

3. Organisms whose morphology, and fermentation tests are those of diphtheroids may show positive virulence tests either with or without protection by antitoxin and may give the same reactions with typhoid vaccine and with horse serum as virulent diphtheria organisms.

4. On subcutaneous inoculations of virulent cultures of *B. diphtheriae,* typhoid vaccine does not prevent the death of the guinea-pig nor alter the course of the disease when injected either before or after the inoculation.

5. Horse serum injections (1 c.c. intracardially) given forty-eight hours to immediately preceding the subcutaneous diphtheria inoculation, prevent the death of standard size guinea-pigs, although there is no protection from the development of extensive necrosis at the site of the inoculation in from one to three weeks. Horse serum injections (1 c.c. intracardially) will protect a standard sized guinea-pig if given within five hours after the diphtheria inoculation. After five hours it has no curative or protective value.

6. Horse serum and typhoid vaccine are not interchangeable foreign proteins for guinea-pigs. Typhoid vaccine offers no protection and horse serum has a distinct protective reaction.

7. Study of the leukocyte reactions following the injection of typhoid vaccine in guinea-pigs does not show the typical foreign protein reaction, while horse serum injection gives the typical leukopenia and leukocytosis of both the simple single reaction and the pendulum types found in man. Typhoid protein has not called forth the nonspecific protein response in guinea-pigs. It is of importance in experimental studies in animals of foreign proteins to determine the ability of the species to split the protein to be tested. Antitoxin in 0.25 c.c. volume of horse serum does not cause a similar leukocytosis.

8. Diphtheria inoculation subcutaneously causes a marked leukocytosis and a pendulum swing not unlike that of foreign proteins.

9. Normal horse serum contains a variable number of antitoxin units. The specimen used contains less than 3 units per c.c., and undoubtedly the protective value of horse serum in these experiments is due for the greatest part to the antitoxin content. Yet it is impossible to rule out the probability that in addition there is another factor, which may be that of a nonspecific protein reaction, since egg white

increases the length of life or in isolated cases protects guinea-pigs against virulent diphtheria organisms.

10. The question of the importance of cellular response in non-specific protein therapy is still unsettled. These experiments showing no protection in guinea-pigs by typhoid vaccine which does not give a cellular response, and the protection given by egg white which produces a definite leukocytosis, strengthen the previously stated view of Cowie and Calhoun that the therapeutic results of nonspecific protein in arthritis depend on the stimulation of the mesenchymal fundaments for blood cell production.

11. There is experimentally no sufficient basis for substituting non-specific protein for the specific antiserum treatment of diphtheria infections and intoxications. Antitoxin in the usual dosage is more efficient in every way than horse serum, and should be used by preference when procurable. In extraordinary situations where antitoxin absolutely cannot be obtained horse serum in large doses should be used as a substitute.

12. Even as small amounts of antitoxin as 6 units will protect a 250 gm. guinea-pig against the injection of virulent diphtheria organisms and the value of diphtheria antitoxin in diphtheria is emphasized by the results of these experiments.

SOME EXPERIMENTS TO DETERMINE THE PERSISTENCE OF EXTRANEOUS BACTERIA IN THE GASTRO-INTESTINAL TRACT OF GUINEA-PIGS AS INFLUENCED BY DIET *

A. GRAEME MITCHELL, M.D., AND PAUL LEWIS, M.D.

PHILADELPHIA

INTRODUCTION

It is commonly believed that the character of the bacterial flora of the gastro-intestinal tract has an important influence on health. In certain instances this is unquestioned. The implantation of sufficient numbers of certain bacteria, *B. typhosus, B. dysenteriae* or *Vibrion cholerae* in the absence of a counteracting general bodily immunity brings about the development of the infections specifically related to these organisms. So also, but possibly in a less specific way, the less well characterized gastro-intestinal disturbances of infancy and childhood are commonly supposed to be due either to the activity of particular species of bacteria or to an alteration in prevailing types of micro-organisms.

A relationship between the general type of bacterial flora prevailing in the gastro-intestinal tract and more obscure disorders, such as anemias and ill defined general intoxications, is often surmised, but scientific evidence of such an association cannot be said to have been presented convincingly. None the less, the administration of acid producing types of bacteria with the conception that they will be of benefit in limiting the activity of putrefactive types is widely practiced. A review of the literature leaves it a matter of great doubt whether the administration of the acid producing types leads to more than a most temporary change in the intestinal flora. The experiments of unbiased observers make it probable that after a short period the extraneous bacteria are completely eliminated. Assuming that the prevalence of a type of micro-organism or of a particular species is of favorable significance for the host, it becomes a matter of considerable interest to know on what condition or circumstance the survival of the favored type is possible.

This question is closely related to another of the same general character and of equal importance, namely, the periodic variation in the prevailing type of bacteria in the respiratory tract. Not that the

causes of variation in the respiratory tract are likely to be identical with those in the intestine, but the principles on which these variations take place are likely to have important common features.

The problems involved are of great interest from a biologic point of view. A complete solution of them would doubtless influence practice. What our work has to offer, however, is not a solution—merely a beginning—and a suggestion as to a method of study not previously employed. The work here presented is in a sense an extension of experiments carried out some years ago by one of us (Lewis, unpublished) in the course of which the method of study was used and some of its limitations defined. Aside from outlining a method and the conditions met with as preliminary to experimentation in this field our present paper offers one point which seems to have real interest, namely, that while B. pyocyaneus quickly disappears from the normal gastro-intestinal tract on a normal diet, and does not persist longer when certain obviously unfavorable diets are offered, the addition of certain favorable factors (greens) to an otherwise unsatisfactory diet does tend to favor the persistence of this organism. This may warrant the suggestion that the relationships between particular bacterial species as persistent inhabitants of the intestinal tract and particular articles of diet may be closer than has hitherto been postulated, and this idea may be worthy of further study.

REVIEW OF LITERATURE

The intestinal flora of man and other animals has been studied extensively, and has been of especial interest to the pediatrist. Not only have the types of bacteria been investigated in various intestinal disorders, but the "switching" from a predominance of one type to another has been demonstrated.[1] Briefly stated, an excess of carbo-

---

1. Hull, T. G., and Rettger, L. F.: Further Studies on the Influence of a Lactose-Containing Diet on the Intestinal Flora, J. Bacteriol. **1**:120, 1916. Penrose, C. A.: A Review of the Theories and Facts Underlying the Treatment of Diseases by Soured Milk Cultures, Maryland M. J. **58**:53, 1915. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs Through Diet, J. Med. Res. **39**:415, 1919. Herter, C. A., and Kendall, A. I.: The Influence of Dietary Alterations on the Types of Intestinal Flora, J. Biol. Chem, **7**:203, 1910. Hull, T. G., and Rettger, L. F.: The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora. IV. Diet Versus Bacterial Implantation, J. Bacteriol. **2**:47, 1917. Herter, C. A.: Experimental Variation of Intestinal Flora by Changes in Diet, Internat. Beitr. z. Path. u. Ther. der Ernährungsstörungen **1**:275, 1909. Herter, C. A.: The Common Bacterial Infections of the Digestive Tract and the Intoxications Arising from Them, New York, The Macmillan Co., 1907. Porter, L.; Morris, G. B., and Meyer, K. F.: Certain Nutritional Disorders of Children Associated with a Putrefactive Intestinal Flora, Am. J. Dis. Child. **18**:254 (Sept.) 1919. Distaso, A., and Sugden, J. H.: Entero-Intoxication—Its Causes and Treatment, Biochem. J. **13**:153, 1919. Ford, W. W.; Blackfan, K. D., and Batchelor, M. B.: Some Observations on Intestinal Bacteria in Children, Am. J. Dis. Child. **14**:354 (Sept.) 1917.

hydrate in the diet tends to favor the growth of the acid forming type of bacteria in the intestinal tract, while an excess of protein favors the growth of putrefactive organisms.

Some of Metchnikoff's pupils and followers have published investigations that attempt to support his hypothesis that the lactic acid bacillus is implanted in the digestive tract. Cohendy [2] concluded from the study of four human subjects that the *B. bulgaricus* appeared in the stool from three to five days after the first ingestion of that organism. It was found each day thereafter, and it was still present in the stool from twelve to twenty-four days after the last ingestion. In one of these patients it was revealed by an abdominal operation, which occurred during the course of the experiment, that the *B. bulgaricus* multiplied in the upper two-thirds of the colon. Results similar to these were obtained by Leva. [3] Later Cohendy experimented with thirty other subjects, including himself. In this later work he apparently did not attempt to recover the ingested organism from the stool.

Belonovsky [4] conducted experiments on mice over a period of ten months. After feeding the bulgarian ferment daily to these animals, he recovered the organism in ten days by culturing the stool, and found that it persisted in the intestinal discharges for about four weeks after the return to a normal régime and the cessation of germ feeding. The author states that on examining the excrement under the microscope, there was no predominance of the bulgarian bacillus. Control mice were fed various substances, such as lactic acid, sterilized milk, bulgarian ferment killed by heat, and other organisms (*B. pyocyaneus* and *B. prodigiosus*). It was only in mice fed with *B. bulgaricus* that the total number of bacteria in the droppings was diminished. It was apparently on such evidence as this that Metchnikoff based his claim of intestinal implantation of the bulgarian bacillus, as he himself does not seem ever to have demonstrated such a phenomenon. [5]

---

2. Cohendy, M.: Essais d'acclimatation Microbienne Persistante dans la Cavité Intestinale. Delimitation du Siége Probable de cette Acclimatation, Compt. rend. Soc. Biol. **60**:364, 1906. De la Disinfection Intestinale Obtenue sans Régime Special par l'acclimatation d'un Ferment Lactique dans le Gros Intestin, Compt. rend. Soc. Biol. **60**:602, 1906.

3. Leva, J.: Zur Beurteilung der Wirkung des Lactobacillus und der Yoghurtmilch, Berl. klin. Wchnschr. **45**:922, 1908.

4. Belonovsky, J.: Influence du Ferment Lactique sur la Flore des Excrements des Souris, Ann. Inst. Pasteur **21**:991, 1907.

5. Metchnikoff, E., et al.: Bacteriotherapie, Vaccination, Serotherapie, J. B. Bailliere et Fils, Paris, 1909. Metchnikoff, E.: The Prolongation of Life, New York, Putnam Sons, 1908. Etudes sur la Flore Intestinale, Ann. Inst. Pasteur **27**:894, 1913. We are not concerned here with the question as to whether or not the feeding of the bacillus does good clinically. The subject under discussion is only that of the 'mplantation of organisms in the intestinal tract.

The work of later investigators does not substantiate the theory of implantation.[6] Hull and Rettger performed one hundred and eighty individual experiments on white rats, six on other laboratory animals, and four on man. They collected and cultured the feces, but were unable to establish the *B. bulgaricus* in the intestinal tract, in spite of the ingestion of large numbers of these organisms. Herter and Kendall found that the exclusive feeding of a rhesus monkey for two weeks with milk fermented with the bulgarian bacillus failed to establish the predominance of this organism in the cecal region or in the colon. The experiments of Rahe show that the bacillus bulgaricus is capable of an apparently limited survival in the upper intestine of the monkey. Rahe's results are shown in Table 1.

TABLE 1.—RESULTS OF FEEDING B. BULGARICUS TO MONKEY

Mon-key	Fed	Period of Inges-tion	Time Killed after Last Ingestion	Duod-enum	Jeju-num	Ileum	Cecum	Feces
1	50 tablets per day.........	13 days	24 hours	—	+	—	—	—
2	300 c.c. 48-hr. milk culture.	6 days	7 hours	+	+	+	+	+
3	300 c.c. 48-hr. milk culture.	6 days	7 hours	+	—	—	—	—

More recently the *B. acidophilus,* a normal inhabitant of the intestinal tract of man, has been introduced by mouth in order to prevent the proliferation of the proteolytic types of organisms. It may be said, however, that the proof of the implantation of organisms in the intestinal tract of man or of laboratory animals rests on incomplete evidence.

METHOD OF PROCEDURE

We have approached this subject from a somewhat different angle than previous investigators. The present study is concerned only with the attempt at implantation of an extraneous organism, the *B. pyocyaneus,* in the digestive tract of the guinea-pig. Our aim has been to study the principles governing the implantation, if such can be accomplished. If implantation should not be found possible, we may hope to find out the reasons back of this local immunity. *B. pyocyaneus* has several advantageous characteristics for a study of this kind: it is potentially pathogenic; it produces poisonous substances

6. Rahe, A. H.: A Study of the So-Called Implantation of the Bacillus Bulgaricus, J. Infect. Dis. **16**:210, 1915. Editorial, J. A. M. A. **73**:1844 (Dec. 13) 1919. Herter, C. A., and Kendall, A. I.: An Observation on the Fate of Bacillus Bulgaricus (in Bacillac) in the Digestive Tract of a Monkey, J. Biol. Chem. **5**:293, 1908. Luerssen, A., and Kuhn, M.: Yoghurt, die Bulgarische Saurmilch, Centralbl. f. Bakteriol. **20**:234, 1908 (Quoted by Hull and Rettger, J. Bacteriol. **2**:47, 1917. Heinemann, P. G.: Lactic Acid as an Agent to Reduce Intestinal Putrefaction, J. A. M. A. **52**:373, 1909.

in culture which in its pathogenic relationships it assumes in various character, and above all it is easy of recognition.

The guinea-pig has a comparatively sterile gastro-intestinal tract. This may readily be proved by killing a guinea-pig after a twenty-four hours' fast and taking smears and cultures from the various parts of the intestinal segments. One usually finds a moderate number of organisms in the smear from the stomach; often none from the duodenal smear; a rather large number from the ileum, cecum and colon. Cultures made on agar will frequently show no growth. This negative finding is especially constant in the duodenum. Such a distribution of bacteria corresponds to that found in the intestinal tract of man.[7] If the pig has not been in a state of fast and has a gastro-intestinal tract full of food, organisms found by smear and culture are more numerous, and different molds introduced with the food may grow in the culture. Again, if some time has elapsed between death and the taking of the smears and cultures, the organisms will be correspondingly numerous. The organisms found are gram-positive and gram-negative diplococci and bacilli, the types varying with the diet. (Cultures taken in the manner described show, of course, only the aerobic bacteria). It is possible for certain animals to live with sterile digestive tracts.[8]

The *B. pyocyaneus,* as far as we have been able to ascertain, is not a normal inhabitant of the gastro-intestinal tract of the guinea-pig. Furthermore, this organism has a low pathogenicity, for the guinea-pig can be fed in large numbers mixed with the food without causing ill effects. If fed in the manner as described it seldom enters the blood stream and causes a septicemia. It may, however, gain entrance to the circulation through the intestinal tract.[9] The *B. pyocyaneus* occasionally occurs in the digestive tract of the human apparently in the best of health. In some of our earlier experiments we introduced the *B. pyocyaneus* into the stomach of the guinea-pig by means of a small catheter used as a stomach tube. When a considerable number of organisms were introduced in this manner, the animal died exhibiting a violent gastro-enteritis and a growth of the bacillus was obtained

7. Contributions to the Science of Medicine by the Pupils of William Welch, 1900, p. 543, Cushing and Livingood.

8. Nuttall, G. H. F., and Thierfelder, H.: Thierisches Leben ohne Bakterien im Verdauungskanal, Ztschr. f. Physiol. Chem. **21**:109, 1895; **22**:62, 1896; **23**:231, 1897. Wolmann, E.: Sur l'elevage des Mouches Steriles, Ann. Inst. Pasteur **25**:79, 1911. Cohendy, M.: Experiences sur la Vie sans Microbe, Ann. Inst. Pasteur **26**:106, 1912. Bakteriologische Darmuntersuchungen, Skand. Arch. f. Physiol. **16**:249, 1904. Freeman, L.: Chronic General Infection with Bacillus Pyocyaneus, Tr. Am. Surg. Assn. **34**:113, 1916.

9. Freeman, L.: Chronic General Infection with the *Bacillus Pyocyaneus,* Tr. Am. Surg. A. **34**:113, 1916.

from the heart blood.   If, however, no *B. pyocyaneus* could be recovered from the gastro-intestinal canal, no evidence of gastro-enteritis was observed when the animal was killed, and the culture from the heart was negative.   This method was given up, for the time being at least.

<div align="center">TECHNIC</div>

With the exception of these experiments the technic of the study was as follows: Guinea-pigs that were offered various diets were fed the *B. pyocyaneus* for variable lengths of time.   Later, in order to make the experiments uniform, all the pigs were fed the germ for three days.   A fresh twenty-four hour culture of a strain of the *B. pyocyaneus* which produced a brilliant green color was washed from an agar slant with about 5 c.c. of physiologic sodium chlorid solution and thoroughly mixed with the day's supply of food for the pig.   On cessation of the feeding of *B. pyocyaneus,* nourishment of the pig continued with the various diets unmixed with the organism. At variable lengths of time the pigs were killed and cultures made on agar from the heart blood, the stomach, the duodenum, the ileum, the cecum and the colon.   If the pig died the same cultures were made.   These cultures were incubated for twenty-four hours, and after that kept at room temperature.   No tube was declared negative for the *B. pyocyaneus* until at least five days had elapsed without evidence of green pigmentation.   After having first ascertained that it was the *B. pyocyaneus* with which we were working, an appearance of the green pigment was considered sufficient evidence of the presence of that organism in the cultures.   The + marks in the charts indicate the amount of green pigmentation appearing in the agar, + a small amount of the color; ++ a larger amount, coloring about half the agar slant; +++ when all the agar was permeated with the pigment.

A series of experiments was first undertaken to ascertain whether or not the *B. pyocyaneus* would grow in the gastro-intestinal tract of the guinea-pig, and whether or not diet had any effect on such growth. Previous to the feeding of the *B. pyocyaneus* mixed with the food, the pigs had been fed on their regular diet which consisted of oats and bread mixed with water, hay, and green stuff twice a week.   Of the fourteen pigs used, three were continued on their regular diet and the *B. pyocyaneus* was mixed with the oats, bread and water for two days.   *Bacillus pyocyaneus* was recovered from the cecum of two of these pigs when killed one or two days later, but not from the pig killed four days later.   The remaining pigs in this series were kept on their regular diets until the day on which they received their first *B. pyocyaneus* feeding mixed with their new diets.   They did not take the abnormal diet well, and there is, therefore, some doubt

as to the amount of germ ingested. However, in three of these pigs the *B. pyocyaneus* was recovered either from the ileum or cecum or both, when killed two days after having been previously fed *B. pyocyaneus* for two days. These three pigs had been fed on hay and water, milk and water, and crackers and water respectively. Other pigs in this series had been nourished on crackers and milk, bread and milk, bread and water, oats and water. From the pigs thus fed *B. pyocyaneus* could not be recovered when they were killed two days after the cessation of a two day period during which that organism had been administered with the food.

In order to find out whether the length of time during which the *B. pyocyaneus* was fed had any effect on its persistence in the digestive tract, several pigs were fed with the organism mixed with their regular diet for variable lengths of time (from three to fourteen days) and then killed at intervals of from two to eleven days. In none of these pigs was the *B. pyocyaneus* recovered when cultures were taken from the different parts of their intestinal tract and stomach (Table 2).

TABLE 2.—Results in Pigs Fed on Normal Diet of Oats, Hay, Bread and Green Stuff. B. Pyocyaneus Mixed with This Normal Diet for Variable Lengths of Time. Normal Diet Continued Until Pigs Were Killed or Died

No. Days Pigs Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
2	K	1	....	0	0	0	+	
2	K	2	....	0	0	....	+	
2	K	4	....	0	0	0	0	
3	K	4	....	0	0	0	0	0
3	K	5	....	0	0	0	0	
3	K	6	N.G.—0	0	0	0	0	0
3	K	7	....	0	0	0	0	0
3	K	8	N.G.—0	0	0	0	0	0
3	K	9	N.G.—0	0	0	0	0	0
3	K	11	N.G.—0	0	0	0	0	
7	K	3	....	0	0	....	0	
14	K	2	N.G.—0	0	0	0	0	0

Day killed or died, i.e., day after last ingestion of pyocyaneus. In the columns showing the results of culture, a blank indicates that no culture was taken; O indicates that there was no growth of pyocyaneus; N.G. indicates that there was no growth or any type of organism; + indicates a growth of pyocyaneus.

The thought presents itself as to whether or not much of the pyocyaneus is ingested when the organism is mixed with the regular diet of oats, bread and water, hay and green stuff. It will be remembered that in eating the whole oat the pig cracks open the outer covering of the oat kernel, discards this covering and eats the softer center. By using rolled or crushed oats the culture of *B. pyocyaneus* can be mixed thoroughly with the food. Accordingly, four pigs were fed in this manner. First, they were given a two-day diet of rolled oats without pyocyaneus. This was to accustom them to their diet, or

at least to assure sufficient hunger so that during the three following days in which the *B. pyocyaneus* was fed a considerable amount of the germ-mixed food would be ingested. On discontinuing the feeding of the organism, the regular diet was instituted. The *B. pyocyaneus* was not recovered from any of the pigs of this series when killed at intervals of from five to eleven days later. On the normal diet, *B. pyocyaneus* does not, then, persist in the digestive canal.

Several other experiments were carried out, the details of which need not be given. Briefly, they consisted in feeding series of pigs on a simple died of oat kernels and water. In some of these series the attempt was made to assure the ingestion of the bacillus by mixing it with oats and water eighteen hours or less before feeding. It was found that the organism did not always live under such circumstances.

TABLE 3.—Pigs Fed Rolled Oats for One Week; Then Rolled Oats Plus B. Pyocyaneus for from One to Three Days. A Diet of Rolled Oats Was Then Continued. Three Controls Not Fed B. Pyocyaneus Died at Eight, Eight and Fifteen Days, Respectively

No. Days Pyo. Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
3	D	2	+++	+++	....	....	++	
3	D	2	N.G.—0	+++	....	....	+++	
3	D	3	N.G.—0	0	0	....	++	0
3	K	5	N.G.—0	0	0	....	0	0
3	K	7	N.G.—0	+++	++	0	++	+
1	D	1	N.G.—0	0	0	0	0	0
2	D	2	N.G.—0	++	++	++	+++	++
3	D	3	+++	+++	N.G.—0	+++	+++	+++
2	D	4	N.G.—0	++	++	++	0	
3	D	3	N.G.—0	+	0	++	+++	0
2	K	7	....	0	N.G.—0	0	0	N.G.—0
2	K	9	....	0	0	....	0	0
3	K	9	....	+	++	....	0	0
3	K	9	....	0	0	0	0	0

+   Indicates a slight growth of pyocyaneus.
++   Indicates a more active growth.
+++ Indicates a large amount of growth.

In order to remove doubt as to whether the *B. pyocyaneus* was ingested because of the failure of the pigs to eat an abnormal diet, such as rolled oats, a number of pigs were fed *B. pyocyaneus* only after they had been previously fed on rolled oats alone for a week. Over 50 per cent. of the fourteen pigs in this series died.[10] We believe that it is seldom, if ever, that guinea-pigs die as the result of the ingestion of *B. pyocyaneus* when mixed with the food, but that death is due rather to the lack of essential elements in the limited diet. It will be seen later that the addition of green stuff to the rolled oats partly overcame this difficulty, and that only four of fifteen pigs

10. Three control pigs that were fed simply on rolled oats and water without at any time the admixture of *B. pyocyaneus* died at eight, eight, and fifteen days, respectively, after the institution of the régime.

(about 25 per cent.) died. It is probable from the necropsy findings and the cultures that at least two of these four pigs died from an infection with an organism of the paratyphoid group. *B. pyocyaneus* was recovered from the gastro-intestinal tract of nine of the fourteen pigs (Table 3). Three of these nine pigs died two days after the cessation of pyocyaneus feeding; three died three days after; one died four days after; one was killed seven days after and one was killed nine days after. Of the five pigs in which the *B. pyocyaneus* was not recovered one died at the end of the first day after the attempt to feed *B. pyocyaneus* and this pig was apparently sick at the time with an infection by an organism of the paratyphoid group and did not eat the food mixed with the *B. pyocyaneus*. Of the other four, one was killed at the end of five days, one at seven days and ten at the end of nine days.

In the next experiment a small amount of green stuff was added each day to the rolled oats diet. *B. pyocyaneus* was recovered in all at the end of seven days after the cessation of *B. pyocyaneus* feeding, one was killed nine days after feeding ceased and one was killed thirteen days after feeding ceased. Of the pigs in which *B. pyocyaneus* was recovered, two died the first day after the cessation of pyocyaneus feeding; one was killed after five days; one was killed and one died after seven days; one was killed at eight days; three were killed at nine days; one was killed at ten days; one was killed at eleven days and one was killed at twelve days (Table 4).

TABLE 4.—Pigs Fed Rolled Oats Plus Green Stuff for Five Days; Then Rolled Oats Plus Green Stuff Plus B. Pyocyaneus for from Two to Three Days. A Diet of Rolled Oats and Green Stuff Then Continued

No. Days Pyo. Fed	Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
2	D	1	N.G.—0	+++	+++	....	+++	+++
2	D	1	0	+++	+++	+++	+++	0
3	D	7	N.G.—0	+++	0	++	+++	+
3	D	10	N.G.—0	+	0	....	++	++
3	K	5	+	0	N.G.—0	++	+	0
3	K	7	N.G.—0	0	0	0	0	
3	K	7	N.G.—0	N.G.—0	....	0	+	N.G.—0
3	K	9	....	0	0	0	+++	0
3	K	9	N.G.—0	+++	++	0	0	0
3	K	9	N.G.—0	0	0	0	+	
3	K	9	N.G.—0	0	0	0	0	0
3	K	9	N.G.—0	0	0	0	++	0
3	K	10	N.G.—0	+	0	....	++	++
3	K	11	N.G.—0	0	0	0	++	0
3	K	12	N.G.—0	0	N.G.—0	0	+	0
3	K	13	N.G.—0	0	N.G.—0	0	+	0

Ten pigs were now fed rolled oats and butter for five days, then *B. pyocyaneus* was mixed with this food for three days and the rolled oats and butter diet continued thereafter. In all of this series *B.*

pyocyaneus was recovered from the digestive tract when the pigs were killed or died from three to thirteen days following the cessation of germ feeding. Five pigs died at three, four, seven, nine and ten days, respectively, and five were killed at five, five, seven, eleven and thirteen days respectively (Table 5).

TABLE 5.—PIGS FED ROLLED OATS PLUS BUTTER FOR FIVE DAYS; THEN ROLLED OATS PLUS BUTTER PLUS B. PYOCYANEUS FOR THREE DAYS. A DIET OF ROLLED OATS AND BUTTER WAS THEN CONTINUED

Killed or Died	Day Killed or Died	Heart Culture	Stomach Culture	Duodenum Culture	Ileum Culture	Cecum Culture	Colon Culture
D	3	N.G.—0	0	+	+++	+++	0
D	4	N.G.—0	0	0	....	+++	N.G.—0
K	5	N.G.—0	N.G.—0	N.G.—0	....	++	0
K	5	0	0	0	++	+++	+++
D	7	N.G.—0	++	++	0	++	++
K	7	0	0	0	N.G.—0	+	0
D	9	N.G.—0	+	+++	++	++	0
D	9	N.G.—0	++	++	0	+	0
K	11	N.G.—0	0	N.G.—0	....	+++	0
K	13	N.G.—0	+	++	+	+	++

SUMMARY AND CONCLUSIONS

Bacillus pyocyaneus when fed to guinea-pigs nourished on a diet of oats, hay, bread and green stuff (the normal diet in this laboratory) usually disappears from the gastro-intestinal tract within three days. When oat meal is given as a sole article of diet, the *B. pyocyaneus* has been found at seven and nine days after the last administration. The addition of a small amount of green stuff, or of a certain amount of butter to the oatmeal diet, has apparently prolonged the period of persistence of the bacterium: *B. pyocyaneus* on these slightly amplified diets has been found to persist about two weeks with considerable regularity. This increased persistence is probably apparent only. The animals on a strict oatmeal diet do not live long enough to enable a complete experiment to be carried out much beyond eight or ten days.

Bacillus pyocyaneus could not be recovered from the digestive canal in any case more than sixteen days after the cessation of its ingestion by mouth. Judged by the amount of pigment produced in the culture, the number of surviving bacteria became progressively less the longer the time interval following the cessation of its ingestion by the pig. *B. pyocyaneus* persisted more readily in the cecum than in other parts of the digestive tract, next in the stomach, although it was often found on culturing the duodenum, ileum and colon. This was true whether the pigs were killed soon after the cessation of *B. pyocyaneus* feeding or only after a longer interval.

It is probable, on the basis of these experiments, that there is an effect of dietary deficiency which consists in the depression of a normal mechanism controlling the implantation of extraneous bacteria in the intestinal tract.

AN ANALYSIS OF TWO-HUNDRED AND FIFTY WARD CASES OF ACUTE ENDOCARDITIS IN CHILDREN *

HENRY P. LEDFORD, M.D.

Graduate Student in Pediatrics, Harvard Medical School

BOSTON

An endeavor is made in this paper to analyze a large series of cases of acute endocarditis treated in hospital wards, not so much for the purpose of imparting new information on a subject already much discussed, but to give briefly the etiology, symptoms, physical findings, treatment and immediate results of the treatment as they were recorded in these 250 cases. Only cases of acute endocarditis are included in this series. There are, however, a number of cases of acute exacerbations of chronic valvular disease which resulted from previous attacks of acute endocarditis. The severity of these cases varied considerably. There are seventy comparatively mild cases, which are grouped together as the "mild group." The remaining 180 cases are placed in the "severe group."

ASSOCIATED CONDITIONS AND PREDISPOSING CAUSES

Age.—Morse,[1] Holt[2] and Dunn[3] state that endocarditis is uncommon before the fifth year. In this series, 24.4 per cent. occurred before the fifth year. The greatest incidence, 38.8 per cent., was between the fifth and eighth years. In the group of patients between the ages of 8 and 13 years, there were twenty-three who gave a history of previous attacks occurring before the end of the eighth year, thus bringing the percentage occurring between 5 and 8 years up to 48 and reducing the primary attacks occurring between 8 and 13 years to 27.6 per cent.

Sex.—The sexes as a whole were almost equally affected. Below the age of 5 the males were slightly in the lead, while above 8 years the females took the lead.

Associated Diseases.—Several patients gave a history of tonsillitis, or chorea, or both, in addition to rheumatic fever. All of these I have classed as rheumatic fever. Other patients gave a history of chorea

1. Morse, J. L.: Boston M. & S. J. **161**:273, 1909.

2. Holt, L. E.: Textbook of Pediatrics, Ed. 7, New York, D. Appleton & Co., p. 594.

3. Dunn, C. H.: Textbook of Pediatrics, Troy, N. Y., Southworth Co., Vol. 3 p. 33.

and tonsillitis, which I have classed as chorea. By some writers all these conditions are classed with endocarditis, as different manifestations of the same infection. This theory cannot very well be disproved, as the causative agent in any of the conditions is not known, but the findings in this series of cases would tend to show that, at least, the virulence of the infection differs in the different manifestations. Endocarditis occurring with chorea is found to be much milder than that occurring with either rheumatic fever or tonsillitis: the mortality in the choreic group being only 2.8 per cent., while that of the rheumatic group is 17 per cent. and that of the tonsillitis group 10 per cent.

TABLE 1.—Age Incidence

Years	Cases	Per Cent.
Between 2 and 3	17	6.8
Between 3 and 5	44	17.6
Between 5 and 8	97	38.8
Between 8 and 13	92	36.8

TABLE 2.—Sex Incidence

	Cases	Per Cent.
Male	120	48
Female	130	52

TABLE 3.—Associated Diseases

Disease	Cases	Per Cent.
Rheumatic fever	151	60.4
Chorea	36	14.4
Tonsillitis	30	12.0
Local sepsis	8	3.2
Influenza	4	1.6
Pneumonia	2	0.8
Scarlet fever	2	0.8
No known associated disease	17	6.8

Endocarditis in childhood is largely due to rheumatic fever infection, and it may occur as the first manifestation of that infection. In this series 151 cases, or 60.4 per cent., gave a history of rheumatic fever. In five of these the articular symptoms followed those of endocarditis. Very severe endocarditis may accompany the mildest articular manifestations of rheumatic fever. Five of the fatal rheumatic cases gave a history of very slight articular pains. In seventeen cases there was no history of rheumatic fever, chorea, tonsillitis or other infectious disease. It seems quite probable that these were largely rheumatic cases; the rheumatic pain being so slight that it was unnoticed by the patient. Six of these seventeen patients died, thus showing the severity of this class of cases.

It seems reasonable to believe that the severity of endocarditis, occurring with the mild articular symptoms, can be accounted for by the fact that the patient is not confined to bed by the articular symptoms. Often he is up and about, and in some instances takes violent exercise and becomes aware of disease only when the cardiac symptoms appear; the heart structure being, therefore, severely taxed at a time when the inflammation in the endocardium is at its height.

Thirty-six cases, or 14.4 per cent., gave a history of chorea. This is a much smaller percentage than has been found by many investigators. Eustis [4] reported that 70 per cent. of his cases were associated with chorea. He included all the cases which gave a history of chorea. Holt, in a series of 117 cases, reports 30 per cent. occurring with chorea.

Tonsillitis was the only associated condition found in thirty cases, or 12 per cent. It was present, however, in the majority of the choreic and rheumatic cases. Eight cases, or 3.2 per cent., were associated with local sepsis, including cervical adenitis, osteomyelitis and empyema. Pneumonia was found to be the only associated condition in two cases and both these patients recovered. Four cases, or 1.6 per cent., gave a history of influenza. These were very severe cases, two proving fatal. Two cases were due to scarlet fever and both these patients recovered.

SYMPTOMS

There were 104 patients, or 41.6 per cent., who did not at any time complain of any symptoms relative to the heart. These cases came into the doctor's care because of associated diseases, such as chorea, tonsillitis, etc. The most constant symptoms complained of were dyspnea, precordial pain, palpitation and epigastric pain. Dyspnea was a marked symptom in 115 cases, or 46 per cent. Precordial pain was present in forty-four cases, or 17.6 per cent. Thirty-one patients, or 12 per cent., complained of epigastric pain. Palpitation was complained of by only fourteen patients, or 5.6 per cent. Sixty-one per cent. of the rheumatic group, 56.6 per cent. of the tonsillitis group, 19.4 per cent. of the choreic group and 90 per cent. of the remaining groups complained of cardiac symptoms. Twenty-one per cent. of the patients classed in the mild group and 72.7 per cent. of those in the severe group complained of cardiac symptoms.

Temperature.—The temperature was found to be very irregular in the majority of cases. I have, therefore, tabulated each patient's average temperature during the febrile period of the disease. The temperature of the group as a whole was very moderately elevated, the average being 99.8 F.

The average temperature for the severe group was 100 F., that of the mild group 99.1 F., that of the fatal group 100.3 F.

---

4. Eustis, R. S.: Boston M. & S. J. **173**:348, 1915.

In the severe group, 55 patients had an average temperature of 99 F.; 74 had 100 F.; 32 had 101 F.; 15 had 102 F.; 4 had 103 F.

In the fatal group 12 patients had an average temperature of 99 F.; 10 had 100 F.; 5 had 102 F.; 1 had 103 F.

In the mild group there were only fourteen patients with a temperature of 100 F., or above. The average duration of the febrile period in the severe group was more than double that of the mild group, being thirty-six days in the severe group and seventeen days in the mild group. The duration of the febrile period was longer in the older patients, as shown in the following table:

Age	Duration, Days
Below 3 years	18
Between 3 and 5 years	27
Between 5 and 8 years	35
Between 8 and 13 years	47

Pulse Rate.—The pulse rate in individual cases was found to be very irregular. I have, therefore, tabulated each patient's average pulse rate during the febrile period (Table 4).

TABLE 4.—PULSE RATE IN VARIOUS GROUPS

Number of Patients	Pulse Rate per Minute
Mild Group:	
55	90
11	100
4	120
Severe Group:	
44	100
21	110
59	120
36	130
15	140
Fatal Group:	
3	100
1	110
14	120
15	130
4	140
3	150

Cardiac Enlargement.—In recent years the diagnosis and prognosis of heart disease is largely made from one finding, cardiac enlargement. Therefore the importance of this sign has stimulated a desire for more accurate means of determining the outlines of the heart. Much has been done with the roentgen rays to check up percussion findings, and to perfect a method of obtaining accurate outlines.[5] Although it has been proven by roentgen-ray interpretations that percussion outlines

5. Shattuck, G. C.: Boston M. & S. J. **174**:301. Holmes, G. W.: Med. Clin. N. America **1**:1197, 1916.

are often erroneous in adults, this is not true with children, if their chest walls are not deformed. Children have comparatively thin chest walls, and percussion is, therefore, less difficult and more accurate than in the chests of adults. In this series percussion was used entirely for locating the cardiac outlines. I have tabulated only the greatest transverse diameter of relative cardiac dullness. For the purpose of comparison I will first give the normal diameters as they are found at various ages.[6] The normal transverse diameter of relative cardiac dullness in infancy is from 7 to 8 cm.; at 6 years it is 9.5 cm., and at 12 years it is 11 cm. The transverse diameter of relative cardiac dullness, as found in the various groups of this series, is shown in Table 5.

TABLE 5.—TRANSVERSE DIAMETER OF RELATIVE CARDIAC DULNESS

Group	Below 6 Years		Between 6 and 8 Years		From 8 to 13 Years	
	Diameter, Cm.	Cases	Diameter Cm.	Cases	Diameter, Cm.	Cases
Mild...........	9	6	10	13	10	10
	10	3	11	5	11	12
	11	2	12	2	12	10
	13	1	14	1	13	1
					14	4
Average....	10	....	10.7	....	11.4	
Severe.........	9	12	9	3	9	2
	10	17	10	6	10	6
	11	17	11	12	11	12
	12	8	12	15	12	13
	13	4	13	16	13	13
	15	4	14	3	13	8
			15	2	14	3
					15	2
					16	2
					18	2
Average....	10.6	....	12	....	12.5	
Fatal..........	9	2	12	2	10	2
	10	3	13	5	13	4
	11	3	14	2	14	4
	12	5	15	1	15	2
	13	2	18	1	18	1
	15	1				
Average...	11.5	....	13.5	....	13.7	

White Blood Count.—The leukocyte count in this series varied greatly. While the increase was marked in some cases, there were others in which the absolute counts showed little or no deviation from the normal. A reason for this apparent incongruity was not always manifest, but as a rule, the degree of severity of the infection, together with certain etiologic factors, determined to a large extent the amount of leukocytosis. I have been unable to find very much in medical literature concerning the reaction of the leukocytes in endocarditis.

6. Taken from Morse's Case Histories in Pediatrics, Ed. 2.

Cabot,[7] in a series of twenty-six cases, which he termed acute ulcerative endocarditis, found the initial leukocyte count below 10,000 in six cases, between 10,000 and 15,000 in five cases, and above 15,000 in fifteen cases. The lowest count was 3,000 and the highest 34,000.

In another series of fourteen cases, which he called benign endocarditis, he found the leukocyte count much higher than in the ulcerative group just cited. In this group the count was below 15,000 in only one case, betweeen 15,000 and 20,000 in three cases, and above 20,000 in the remaining ten cases, the lowest count being 12,000 and the highest, 50,100. These extremely high counts occurring in cases of simple endocarditis must have been due to some associated infection outside of the heart. Unfortunately, systematic counts in large series are not available.

TABLE 6.—Average Initial Count

	Leukocytes
For the whole group of 250 cases	17,200
Below 5 years	18,000
Between 5 and 13 years	17,000
Mild group	13,400
Severe group	19,000
Fatal group	21,000
Rheumatic group	18,000
Tonsillitis group	17,000
Chorea group	11,900
Undetermined group	17,000
Scarlet fever group	14,500
Local sepsis group	22,100
Pneumonia group	28,000
Influenza group	24,000

TABLE 7.—Individual Leukocyte Counts

Patients	Per Cent.	Leukocytes
Mild Group:		
23	33	Below 10,000
45	64	Between 10,000 and 20,000
2	3	Above 20,000
Severe Group:		
23	12.5	Below 10,000
93	52	Between 10,000 and 20,000
64	35.5	Above 20,000
Fatal Group:		
0	0.0	Below 10,000
11	27.5	Between 10,000 and 15,000
5	22.5	Between 15,000 and 20,000
20	50	Above 20,000

It is shown by Table 6, first, that the degree of leukocytosis in acute endocarditis is considerably increased; second, that the count in the cases which are classed as severe, is almost one and one-half times that of the cases classed as mild.

Table 7 presents the individual counts as recorded in the various groups.

---

7. Cabot, R. C.: Clinical Examination of the Blood, Ed. 5, New York, William Wood & Co., p. 347.

These figures show that the leukocyte count is much higher in the severe cases. The few high counts in the mild cases may be accounted for by associated local sepsis, or other associated infections. The low counts recorded in the severe cases are probably due to an overwhelming infection.

It is interesting to note that, among the fatal group, there were no counts below 10,000 and 50 per cent. were above 20,000. The extremely low count in the choreic group is very striking, it being only slightly above normal and a little less than two-thirds as high as the count in the rheumatic fever group. The degree of leukocytosis was not influenced to any appreciable extent by the age of the patient; neither was it affected to a great extent by the degree of fever.

Valvular Involvement.—Endocarditis in children nearly always affects the mitral valve. The aortic valve is affected much less frequently, and is usually accompanied by mitral involvement. Any one or all the valves of the heart may be involved, but in this series there was no instance in which the pulmonic valve showed any physical signs of involvement. There was only one case in which the tricuspid valve was involved and this occurred in a girl, aged 3½ years. She had a severe attack of tonsillitis with rheumatic fever, and died four days after entering the hospital. The mitral valve was also involved in this case. In this series of 250 cases the mitral valve was involved in every instance, and the aortic in thirty-seven instances.

Dunn,[3] in a series of 262 cases of chronic valvular disease of the heart, found the aortic valve alone involved in one instance, and twelve cases in which both the aortic and mitral valves were involved, and no case with tricuspid inolvement. Wentworth,[8] in a series of 600 heart cases, found fifteen of aortic involvement, two of which were not associated with any other lesions, and one instance of tricuspid involvement. In 150 necropsies on children dead of cardiac disease, Poynton[9] found the mitral valve involved in 149 instances and the aortic in fifty-one instances. Fifty per cent. of the cases with aortic involvement were among the fatal cases in this series.

When discharged from the hospital, there were only two cases which did not have a cardiac murmur. Pericarditis occurred in 32 patients, or 12.8 per cent. Seventeen, or 53 per cent. of this number died. Both the aortic and mitral valves were involved in fifteen instances, or 47 per cent. The etiology was rheumatic fever in twenty-five cases, tonsillitis in one case, and influenza in one case. Six cases, or 19 per cent., occurred before the fifth year, and twenty-six cases occurred between 5 and 15 years.

8. Wentworth, M. H.: Boston M. & S. J. **174**:158, 1917-1918.
9. Poynton, M. J.: Brit. M. J. **2**:147, 1918.

FACTORS BEARING ON PROGNOSIS

Age.—It is generally conceded that the earlier the primary endocarditis occurs, the better is the ultimate prognosis, because of the more perfect adaptation of the child to the heart, and the heart to the child; that they grow up together, and are more apt to adapt themselves to each other than they are in later life. The immediate prognosis, however, is much worse in the younger children. The immediate mortality in this series, as a whole, was 16 per cent.; below the third year, it was 30 per cent.; below the fifth year, 23.7 per cent.; between the fifth and thirteenth years 13.7 per cent., thus showing a decreasing mortality with increasing age of the patient.

Sex.—Sex did not seem to influence the severity of the infection, the fatal cases being about equally divided between the sexes.

The type, severity and duration of the infection of the heart itself, influence the prognosis very greatly.

The immediate mortality in the various groups was as follows: acute rheumatic fever, 17 per cent., tonsillitis, 10 per cent., chorea, 2.8 per cent. It appears, therefore, that endocarditis occurring with chorea and not associated with rheumatic fever is very mild, rarely producing death, while in rheumatic fever the prognosis depends on the severity of the cardiac infection. All grades of severity are met with in rheumatic heart infection. A simple rheumatic infection may lead to a slight crumpling of a valve and a soundly healed scar, the process becomes stayed, the heart muscle remains intact, and the heart for practical purposes is little or no worse than a normal heart. A further degree shows mere destruction and greater regurgitation, with involvement of the heart muscle. The next degree is that of repeated acute infection or chronic continuous infection, leading to stenosis and to serious carditis.

How are we to determine the intensity of cardiac infection? European writers are inclined to believe that all diseased hearts become enlarged, that no heart is diseased unless it is enlarged, that the mere regurgitation of blood is insufficient to give rise to dilatation and hypertrophy of the heart, and, therefore, they disregard all apical systolic murmurs unless they are accompanied by cardiac enlargement, the degree of enlargement being proportionate to the intensity and duration of the infection.

Fever.—The height of the fever is not a sure index of the severity of the cardiac infection. The duration of the fever is very significant, however. An early permanent return of the temperature to normal is a very favorable sign. A long duration of fever means that the heart is working under great stress, and that the damage to the heart muscles, especially to the conducting paths, to the interventricular nodes and to

the bundle of His, is in proportion to the duration of the fever. In this series, although the average temperature of the severe and fatal groups was less than one degree higher than that of the mild group, yet the average duration of the fever in the severe group was three times that of the mild group.

Pulse Rate.—The pulse rate is usually higher in the severe cases, but may be as low as 100, even in fatal cases.

Leukocytosis.—Leukocytosis is usually greater in the severer cases, but may occasionally be very slight in cases of marked severity. The average leukocyte count in the severe group was one and one-half times that of the mild group. The process in the heart should be considered active until the leukocyte count has reached normal. Simple mitral regurgitation, without stenosis, may leave the heart little or not at all damaged.

Stenosis.—When stenosis is present, a long continued infection or an often repeated acute infection has already wrought much damage to the heart muscle, the functional efficiency of the heart muscle is much lowered and the ultimate prognosis is, therefore, very unfavorable.

When both aortic and mitral valves are involved, the immediate prognosis is bad and the ultimate prognosis is very much worse.

Heart Failure.—When there are objective signs of heart failure, such as dropsy, enlarged liver and orthopnea, which do not disappear, the patient's future may be recorded in months.

Finally, it is to be clearly recognized, that each case requires special study. The personal element and the patient's daily routine enter largely into the composition of the disease picture. It is manifest, for example, that an impaired heart in the child who has a comfortable home and may lead a life of leisure has a significance different from that of an impaired heart in a child compelled to lead a strenuous and poorly directed life.

TREATMENT

The treatment in these cases consisted largely of rest in bed. Everything else was considered subordinate. The patients were kept as nearly flat in bed as possible, judgment being used in this connection, however, because being kept flat may cause so much fretting and fussing that more strain will be brought on the heart than if the patient is allowed to sit up in bed and play with toys. The severely ill patients were not allowed to feed themselves but were fed in order to prevent even that slight exertion. If there was severe dyspnea or orthopnea, they were propped up with pillows so that they might assume the most comfortable position. There was not a set period of time for all patients to remain in bed, this being determined in each individual case by the duration of the symptoms and the reaction of the heart to exer-

cise.   When the temperature had become normal and the cardiac symptoms showed that the acute infection had subsided, the strict rest treatment was very gradually relaxed, the patient being observed closely.

When the acute symptoms had definitely and permanently subsided the patients were discharged from the hospital.   The patients in whom the symptoms were slightly active were sent to institutions especially provided for their care.   The patients with inactive lesions were discharged home to be followed up by the social service and seen at frequent intervals by the out-patient department of the hospital.

For two or three months the patients were given a limited amount of exercise, being kept in bed the greater part of the time.   During the next one or two years the amount of exercise was limited, and finally an effort was made to plan the whole life so as to save the heart.

The nutrition and physical condition were kept in the best possible state, because the nutrition of the heart muscle depends to a considerable extent on the general nutrition.

The patients in the mild group were kept in bed in the hospital an average of 30.5 days, and those in the severe group an average of 50 days.

The general measures of treatment employed in the hospitals were those for acute infectious diseases in general.   The bowels were kept open, and the diet consisted at first of milk and starchy foods; later meat and eggs were allowed.   In cases occurring with acute rheumatic fever, acetyl salicylic acid was given freely.   Digitalis was used very infrequently, being given only in the cases of chronic valvular lesions with failure of compensation.   It was not given in cases of simple acute endocarditis.   Sedatives were used when demanded.   When the heart was irritable and the action rapid, and especially if there was precordial pain, an ice bag was applied over the heart.   Other symptoms were treated as they arose.

When the focus of the infection could be located, it was, as a rule, removed before the patient was discharged from the hospital.   It was difficult sometimes to determine just when the focus should be removed.   If the acute symptoms gradually cleared up with the focus present, it was not removed until the acute symptoms had subsided. If it was thought, however, that the local focus was keeping the acute symptoms active over an extended period of time, and the condition of the patient was not too bad, the focus was removed.   The teeth and tonsils were the most frequent local foci of infection.   Ether anesthesia was administered without hesitation for tonsillectomies and for teeth extraction, when necessary.   No bad results occurred so far as the heart was concerned.

IMMEDIATE RESULTS OF HOSPITAL TREATMENT

One hundred and six patients, or 42.4 per cent., were discharged home, without active symptoms, to be supervised and cared for by the Social Service and the Out-patient Department of the hospitals. Sixty-seven patients, or 26.8 per cent., were discharged with slightly active symptoms, to institutions provided for this class of cases. Thirty-seven patients, or 14.8 per cent., were discharged against advice with active symptoms. This demonstrates the difficulty in obtaining the cooperation of the parents so necessary in the prolonged treatment of this disease. The remaining forty patients, or 16 per cent., died

STUDIES IN SPASMOPHILIA

III. BLOOD CALCIUM AND CALCIUM THERAPY IN OLDER CHILDREN WITH THIEMICH'S SIGN *

LUDO VON MEYSENBUG, M.D.

Teaching Fellow in Pediatrics, University of Minnesota Medical School

MINNEAPOLIS

We are now perfectly familiar with the low calcium content of the blood in tetany. MacCallum and Voegtlin [1] were the first to demonstrate this in parathyroidectomized dogs; MacCallum and Vogel later confirmed it [2] and the fact was conclusively shown in infantile tetany by Howland and Marriott [3] in 1918. Since that time many investigators have confirmed these results. We are also familiar with the effect of calcium therapy on the blood calcium and the electrical reactions of tetany.

Stheeman [4] reported low blood calcium in older children with anodal reactions of Thiemich, but, as previously pointed out,[5] his method of calcium determination was faulty and his findings inconstant. Howland and Marriott [3] have determined the serum calcium of infants with anodal hyperexcitability but without tetany, and found the average value for twelve cases to be 9.25 mg. per 100 c.c., which is slightly below their normal value of from 10 to 11 mg. Ten of these children, however, had rickets, and they state that in rickets one finds a slightly reduced serum calcium. In fact, the only patients in this group who did not have rickets had 10.7 mg. calcium each.

In the effort to establish the significance of so-called anodal hyperexcitability reactions in older children, blood calcium was determined in such cases and the electrical reactions were studied before and after repeated large amounts of calcium feeding. The problem is not, how-

1. MacCallum, W. G., and Voegtlin, Carl: On the Relation of Tetany to the Parathyroid Glands and to Calcium Metabolism, J. Exper. M. **11**:118 (Jan.) 1909.

2. MacCallum, W. G., and Vogel, K. M.: Further Experimental Studies in Tetany, J. Exper. M. **18**:618 (Dec.) 1913.

3. Howland, J., and Marriott, W. McK.: Observations on Calcium Content of Blood in Infantile Tetany and on the Effect of Treatment by Calcium, Quart. J. M. **11**:289 (July) 1918.

4. Stheeman, H. A.: Spasmophilia of Older Children, Jahrb. f. Kinderh. **86**:42, 1917.

5. Von Meysenbug, L.: Studies in Spasmophilia. II. Electrical Reactions of Older Children, Am. J. Dis. Child. (to be published).

however, as simple as it would appear to be at first glance. There are several complicating factors. The first of these is the fact that the blood calcium may be as low as 70 mg. per 100 c.c. serum without tetany appearing, as shown by Binger [6] experimentally, and corroborated by the findings of Howland and Marriott clinically. When the blood calcium fell below this level tetany supervened. Furthermore, Denis and Minot [7] have pointed out that it is impossible to increase the blood calcium by massive calcium feeding when the initial value is normal. It would seem most unlikely, therefore, that calcium feeding would influence the electrical reactions if these accompany a normal blood calcium.

TABLE 1.—Controls. Calcium Expressed as Mg. Per 100 C.c. Plasma

Age, Yrs.	Date, 1920	C C C	A C C	A O C	C O C	Calcium
4	March 23	2.0	>5	>5	>5	11 3
4	March 23	2.0	3.0	>5	>5	11.5
5	March 26	2.5	>5	>5	>5	11.1
1	March 30	2.6	>5	>5	>5	11.5
5	April 6	2.0	4.0	>5	>5	10.7
Average	....	.....	...	...	...	11.2

TABLE 2.—Thiemich's Sign. Calcium Expressed as Mg. Per 100 C.c. Plasma

Age, Yrs.	Sex	Date, 1920	C C C	A C C	A O C	C O C	Calcium
4	♂	March 23	0.6	2.0	1.4	>5	10.3
5	♂	March 26	1.6	3.0	3.0	>5	10.7
½*	♀	March 26	0.2	1.0	1.0	2.0	11.5
5	♂	March 26	1.4	4.8	2.5	>5	10.9
3	♂	March 27	1.2	3.2	2.4	>5	11.3
2	♂	March 27	1.0	4.5	2.0	>5	10.0
5	♀	March 30	0.6	2.0	1.4	>5	11.4
4	♂	March 30	1.6	3.4	2.4	>5	11.5
1†	♀	March 30	1.4	3.0	1.8	>5	8.7
6	♀	April 2	1.2	3.0	1.6	>5	10.2
5	♀	April 2	1.2	3.2	1.6	C C T 4	11.3
4	♀	April 2	1.6	3.4	3.2	>5	11.7
Average...							10.8

* Rickets.   † Slight rickets.

BLOOD CALCIUM

The cases which I selected were those showing the most marked Thiemich's and Chvostek's signs. The calcium was determined by Lyman's method on citrated plasma.[7] A group of five children with very low electrical irritability was selected as controls.

Table 2 shows the electrical reactions and plasma calcium of twelve children with Thiemich's sign. It is interesting to note that one of

6. Binger, C.: Toxicity of Phosphates in Relation to Blood Calcium and Tetany, J. Pharmacol. & Exper. Therap. **10**:105 (Aug.) 1917.

7. Denis, W., and Minot, A. S.: Effects of Feeding with Calcium Salts on the Calcium Content of the Blood, J. Biol. Chem. **41**:357 (March) 1920.

the highest calcium values found was in an infant 6 months old, with very marked spasmophilic reactions, but without tetany. Five months previously this infant had had convulsions and laryngospasm. The difference between the average values of Table 1 and Table 2 is too slight to be of any significance.

CALCIUM THERAPY

Two children, whose plasma calcium was found to be 10.3 and 11.4 mg. per 100 c.c. respectively (Nos. 1 and 7 in Table 2) were chosen because of the older children they showed the highest electrical irritability and both had very marked Chvostek signs. Table 3 shows the results. S. W. appears to be somewhat improved March 23, after three consecutive days of calcium feeding, but the change is not greater than might be expected in the variation of the reactions from day to day. The reactions of H. T. remain practically constant throughout. The constancy of the plasma calcium is well shown by the analyses on H. T., one taken during the feeding period of massive doses of calcium, the second a week after the calcium had been omitted.

TABLE 3.—CALCIUM LACTATE BY MOUTH

Name, Age and Sex	Date, 1920	C C C	A C C	A O C	C O C	Therapy	Plasma Calcium, Mg. per 100 C.c.
H. T. 4 yrs. ♂	March 9	1.0	3.4	2.0	>5		
	March 15	1.2	3.0	2.0	>5		
	March 15	...	...	...	...	6.0 gm. daily	
	March 16	1.0	2.4	1.6	>5	6.0 gm. daily	
	March 17	1.2	2.8	1.8	>5	6.0 gm. daily	
	March 18	1.0	2.0	1.6	>5	6.0 gm. daily	
	March 19	...	...	...	...	Omitted	
	March 20	0.6	2.2	1.6	>5	6.0 gm. daily	
	March 23	0.6	2.0	1.4	>5	6.0 gm. daily	10.3
	March 30	1.0	2.4	2.0	>5	Omitted March 23	10.4
S. W. 5 yrs. ♀	March 9	0.8	2.0	1.6	>5		
	March 15	1.4	2.0	1.6	>5		
	March 15	...	...	...	...	6.0 gm. daily	
	March 16	1.2	2.0	1.4	>5	6.0 gm. daily	
	March 17	1.0	2.1	1.5	>5	6.0 gm. daily	
	March 18	0.8	2.0	1.2	>5	6.0 gm. daily	
	March 19	1.2	2.0	1.8	>5	Omitted	
	March 20	0.8	2.0	1.4	>5	6.0 gm. daily	
	March 23	1.6	2.4	2.0	>5	6.0 gm. daily	
	March 30	0.8	2.0	1.4	>5	Omitted March 23	11.4

SUMMARY

1. Plasma calcium was determined by Lyman's method on five children with very low electrical irritability and on twelve children with Thiemich's sign. The average value for the first group was found to be 11.2 mg. per 100 c.c., for the second group 10.8 mg. per 100 c.c.—an insignificant difference.

2. Calcium lactate in 6.0 gm. daily doses was fed to two children with Thiemich's sign without resultant change in the electrical irritability.

CONCLUSIONS

1. Thiemich's sign in older children is not based on lowered blood calcium.

2. Calcium feeding in large amounts does not influence the anodal reactions of older children.

RUMINATION IN CHILDREN *

AUGUST STRAUCH, M.D.

Attending Physician at the Cook County Hospital, Children's Department;
Instructor in Medicine (Pediatrics), Rush Medical College

CHICAGO

REPORT OF CASE

History.—William L., born Oct. 6, 1918, is the only child of healthy though nervous parents. The mother is a pianist. Allaitement mixté during the first five months of life; then cow's milk alone for one month. At the age of 6 months, beef soup was repeatedly tried, but soon discontinued because with fits of anger he would persistently refuse it or spit it up. However, cereals, vegetables and fruits were taken well. At the age of nine months, beef soup was tried again and well taken and borne, if mixed with a little milk. There was never any other difficulty in feeding, except that even at the present time soup is disliked. Appetite, digestion and sleep always have been good.

At the age of 15 months (about Christmas, 1919) the boy began to spit up the orange juice that he was wont to take daily since his fourth month of life and of which he was very fond. At this time there was much drooling. At first the spitting up occurred only occasionally, but later it occurred frequently. Then the mother noticed that the boy would reswallow the orange juice after it had come up into the mouth, and that he seemed to enjoy it. He would even put his fingers into the vomitus on the floor and re-introduce it into the mouth. Two months later also other food was "spit up" after almost each meal. The food would ascend into the mouth in small portions without difficulty, violence or nausea, about five minutes after the meal and after a few masticatory movements be reswallowed. A minute or so later it would reappear, and the repetitions of the act were kept up for one hour or longer, also during his playtime. There was little food lost in this process. Parts of food that happened to spill over the clothes were put back by him into his mouth with his fingers. There was no doubt but that the boy enjoyed ruminating. The food brought up never had any odor. After dinner, when the boy used to remain alone and awake for a longer period, there was usually an aggravation of rumination and it also was observed that the "spitting up" became worse whenever the father coughed and belched in the boy's presence, who also manifested a great imitative tendency. On the other hand, rumination was less likely to occur after breakfast when the boy was usually entertained and diverted by his father's fondling and playing with him; or when he was outdoors, which he enjoyed. His appetite and digestion during this whole time was perfect.

The boy is very well nourished, sturdy looking, has red cheeks, weighs at present (at the age of 18 months) 25 pounds, but is very willful, nervous, timid, easily startled and scared by noises and overcautious toward strange persons and objects. His mother considers him a very intelligent though "very queer" child.

Treatment.—Naturally the observation of the influence of psychic elements on his rumination suggested distraction in a systematic manner as a therapeutic measure. In order to deflect his attention intensely and permanently from his affliction various means had to be employed, as exemplified in the following procedures.

March 30, the first day of treatment: Soon after the breakfast, at 6:15 a. m., he began to ruminate as usually. This was immediately stopped when the mother energetically scolded and threatened him. She then sang to him

and got him to sing with her for awhile; thereafter she amused him by questions that he would answer and continued diverting his mind by dressing him. Then the father undertook his amusement so that the boy's mind was permanently occupied for one whole hour. No rumination had occurred. At 10 a. m., after the bath, the boy was fed and put to bed where he fell asleep immediately without rumination. The next feeding was at 1:15 p. m. Immediately thereafter he was amused for about the first ten minutes by songs, in which he eventually joined. Thereafter he was given a new plaything, the novelty of which interested him intensely for awhile. When the novelty began to wear off, he was taken outdoors, which had been observed to have a tendency to lessen his rumination as stated before, no doubt likewise through diversion. No rumination occurred.

At 4:45 p. m. water and orange juice were given. The mother at once sang to him and played on the piano, of which he always has been very fond, and later she played with him. No rumination occurred.

Supper was at 5:30 p. m. He soon ruminated three times, but stopped when scolded. Talking to or continuously playing with him prevented him from ruminating entirely until he finally was put to bed and fell asleep immediately.

During the following few days identical pedagogic-therapeutic procedures were taken. March 31 rumination took place four times after dinner and once after supper. April 1 and 2 it occurred only once after supper. Since that time he has never ruminated or regurgitated. But he began chewing his sleeves or other parts of his garments within reach of his mouth.

In this case the persistent vomiting and regurgitating of soup with angry refusals, apparently due to aversion to it, may be taken as an early symptom of a certain lability of the reflex mechanism of the pharynx, esophagus and stomach under conditions that point to the interference of a psychoneurotic element. The psychic factor also revealed itself by the fact that later, coloring the soup with a little milk induced this very willful, undoubtedly nervous boy to take it without further trouble. There was never any other disturbance of the gastro-intestinal tract. No doubt the responsiveness of the reflex apparatus rendered it possible that later the regurgitation of orange juice, perhaps at first accidental, should have repeated itself with such readiness, in the beginning only occasionally, but soon regularly. The juice being agreeable to him, he apparently learned to reswallow it readily. Such a selective regurgitation of a particular food is well known in the adult ruminant. By frequent repetitions of this process aided by the psychic factor, through facilitation of the nervous centers involved, regurgitation and reswallowing became a pathologic, well fixed nervous habit, a pathologic reflex, easily started and finally released also for gratification by other food. It is not without significance that after the cure the boy, in order to obtain some gratification, found a substitute in chewing his sleeves, for several weeks.

The conception of pathologic conditional reflexes in the sense of Czerny and Ibrahim brings rumination nearer our understanding;

their nature and development was dwelt on by me in a former article.[1] The abnormal motor process of a pathologic condition reflex often originates from local pathologic causes but nevertheless persists even after the subsidence of the primary pathologic stimulus as a kind of pathologic habit of the nervous system. The acts are then provoked by the physiologic stimuli of the daily life. A conditional reflex can be traced to the cooperation of a psychic factor with an ordinary unconditional reflex. There is no definite or characteristic anatomic basis for rumination and its essential initial phase, the regurgitation.

The few fluoroscopic examinations made in babies have demonstrated no gross deviations from the normal and findings of pylorospasm as in the cases of Lust[2] and Aschenheim and in the one reported by me have only an indirect though important bearing. In such circumstances the rumination develops most probably as a secondary functional affection in consequence of the vomiting and regurgitating caused by these diseases. Similarly, "habitual vomiting" and pure regurgitation and vomiting due to chronic dyspepsia, especially often following ablactation, have been complicated by pronounced rumination. The original disturbance, anatomic or functional, sometimes, perhaps, very insignificant and thus easily overlooked, may act merely as an initial factor in the evolution of the pathologic complex of rumination. The members of the motor chain become firmly linked together as a complex and fixed through repetition and facilitation, possibly aided by the desire for gratification that lies in rumination, and may outlast the original affection, appearing then as an independent "neurosis."

The cooperation of an organic and neuropsychic component, combined in varying proportions, may be unmistakable in the development of rumination. In a number of cases it must be admitted, as Landé[3] has pointed out, rumination has developed without a period of previous vomiting (cases of Wirtz, Puoliot). The basis, it seems, is a neuropathic constitution manifesting itself not only in the disturbance of the reflex processes of the automatism of the stomach but also otherwise. Indeed, the presence of various nervous symptoms has been noted by many observers. The psychic factor in my case, namely, the fondness for orange juice and other regurgitated food, suggests itself as a contributory factor.

We know also from observing ruminants that rumination is often enjoyed and that they may regurgitate and ruminate at will, starting the process voluntarily.

1. Strauch, A.: J. A. M. A. **65**:678 (Aug. 21) 1915.
2. Lust: Monatschr. f. Kinderh. **6**: 1911.
3. Landé: Monatschr. f. Kinderh. **14**:196, 1916.

A perfect dependency of regurgitation and rumination on will and intention I repeatedly observed in a friend of mine, a merchant, aged 37 years, a man of unusual intelligence and learning. He has always enjoyed good health and digestion. He cannot recollect at what age his "peculiarity" started, but he remembers with certainty that when about 20 years old he could voluntarily and easily vomit or regurgitate food, and that often he did rechew and reswallow it. He thought it to be natural until told the contrary by his brother in law, who accidentally discovered his habit about that time. He also remembers that he often astonished his friends by the amount of beer he could drink without intoxication; for he readily would empty his stomach and begin anew to drink, his ability to regurgitate having been kept secret from friends and members of his family. Though ruminating was practiced more or less habitually at the time, at the present it occurs only infrequently, but always voluntarily, more or less consciously and he can easily desist from it, as, for instance, when in society. He would regurgitate and ruminate especially after a very heavy meal, or if he had eaten "food hard to digest," as, for instance, tendinous parts of meat, large pieces of potatoes, swallowed in a hasty meal, lettuce mixed with onions, parts of the stem of lettuce, tough fibers of string beans, the white skin of oranges and the skin of sausage. These parts have "a special irritating influence on his stomach, and cause him a peculiar sensation of fullness but no pain or feeling of pressure." He notices "that the food is indigestible." Under such circumstances, he would rechew and reswallow the regurgitated food but spit out the "indigestible parts, as fibers, etc." and stop regurgitating when no more indigestible particles are felt in the ascending food, or the latter begins to taste sour. He also spits out any desired amount of regurgitated food whenever he thinks "it would be better for him to empty the stomach" or if he fears "the food may not agree with him." He would, after an excessive consumption of coffee during a social evening, out of fear that it would disturb his sleep, regurgitate and spit it out immediately after his arrival at home. Regurgitation is easier with a full stomach than with a partly filled one; therefore, to facilitate it in the latter case, he drinks water or swallows air.

Recently I had the opportunity to observe him after a heavy Sunday dinner at the home of a mutual friend. During almost a whole hour, over and over again, complying with my wish, did he demonstrate his ability to regurgitate and ruminate at will. Probably from mental inhibition due to embarrassment he had to drink water in order to facilitate the first act, but thereafter there was no difficulty in bringing up the food as often as he was asked. A very slight strain with the lower part of the abdomen sinking in and the stomach region bulging

out for a moment, while the glottis is closed, and, as he stated, a kind of "pressing up" is done, sufficed to bring the food up promptly. This was somewhat rechewed and then reswallowed; the fibers of stringbeans and celery and parts of lettuce were spit out. He considers his ability to regurgitate a decided advantage, and attributes to it the preservation of his health during a long stay in the tropics despite his overindulgence in frequent club banquets. It is noteworthy that he never was seasick on his many transoceanic voyages.

Imitation in a number of cases has led to regurgitation (Bruns) and also rumination. Freund and Koerner reported two children, aged 3 and 6 years, respectively, who learned this habit from a ruminant governess, but who were soon cured after her dismissal.

As is well known, stimulation of a certain nervous center by peripheral irritation may inhibit other central functions under ordinary physiologic conditions. The experiments of Pawlow's laboratory demonstrated that a conditional reflex likewise may be inhibited by the introduction of a new stimulus. In a similar manner we succeed occasionally in eliminating the pathologic nervous symptom complex entirely, or in part, by the interpolation of an unwonted factor into the reflectoric motor process, as, for instance, in ruminating or habitually vomiting infants (Meyerhofer,[4] Huldschinsky) by feeding thick gruels. Though some authors believe that gruels lessen regurgitation by irritating the gastric mucosa less or on account of the consistency, Schippers[5] emphasizes the psychic factor of a certain food, as his second patient ruminated every food regardless of its consistency, except bean puree. Likewise, the idiotic ruminant of Landé ruminated gruels but kept down vegetables. Schippers' two patients ceased ruminating as often and as long as they were in the roentgen ray room, so that repeated attempts to study the process of rumination roentgenologically failed, it having been impossible to accustom the babies to the room.

Scolding and threatening may stop rumination at least for a short time. We act on a similar physiopsychologic principle if we introduce therapeutically diversion by sounds, play, swinging, change of surroundings as an inhibitory factor and succeed in making the ruminant baby or child desist from his pathologic habit. The less established and inveterate the pathologic mechanism is, the more prompt, ceteris paribus, will be the inhibitory and curative effect of the former · upon the latter. This may explain the prompt therapeutic result in my case.

Wirtz and later Goett[6] and Landé observed the beneficial effect

---

4. Meyerhofer: Therap. Monatschr., April, 1912, p. 262.
5. Schippers: Ztschr. f. Kinderh. **10**:92, 1914.
6. Goett: Ztschr. f. Kinderh. **16**:177, 1917.

of distracting play, and Bruening [7] noticed a child almost immediately cease ruminating when a change of surroundings was effected by giving the patient into individual care. In a case of Somersalo [8] nibbling or sucking a piece of zwieback after meals made the child, who also was given gruels, forget his rumination habit by distraction. However, there are a number of cases that resisted the most varied dietary and intentional or unintentional psychic therapy.

Landé [3] considers rumination in certain cases as "cage disease," long stay in a hospital without diversion and entertainment, the ennui of isolation occasionally creating the affection in her view. Transfer of the patient among lively children, etc., may prove effective therapeutically.

It has long been known that in some adults diversion by animating conversation after meals inhibits rumination and its first phase, the regurgitation and that they may be able to suppress it voluntarily (autosuppression, Boas) the psychic factor of discipline being by all means the principal therapeutic agent. Ylppoe,[9] in whose opinion rumination in infants is often a consequence of aerophagia and its accompanying regurgitation, places the baby on its abdomen in order to prevent air-swallowing during nursing, which position by distraction exerts a psychogenic therapeutic effect. In ruminants that soon became used to this new position and again began to ruminate, the necessary distraction was obtained by placing the children in the abdominal posture on a mobile suspension. The results were excellent, and the author recommends this method also in treating habitual vomiting.

In a ruminating girl, 5 months old, as reported by me, artificial obstruction of the nose by insertion of cotton after each meal while the baby was kept lying down on her back, interfered with rumination and caused discomfort so that she almost entirely ceased even attempting to ruminate, though various methods had previously been employed unsuccessfully. The regurgitation subsided gradually and ceased practically within two weeks. I was led to the systematic use of this "heroic" procedure by the observation that regularly, as often as the nose was pinched, experimenti causa, and nasal respiration thus obstructed, while the baby was kept lying on her back she at once resentfully stopped ruminating and swallowed the food in order to get air through the mouth. One could not help thinking that the child desisted from rumination eventually because of discomfort and urgency of air-hunger entailed by the act, and that after a sufficient

7. Bruening: Arch. f. Kinderh. **60**:116, 1913.
8. Somersalo: Arch. f. Verdauungskrankh. **16**:167, 1920.
9. Ylppoe: Therap. Halbmonatschr. **34**:76, 1920.

time regurgitation itself was given up, because it could no more lead to the pleasurable act of rumination at ease. Unfortunately, soon the baby contracted measles during a ward epidemic and died from complicating bronchopneumonia.

To obtain satisfactory results one must not forget that with nose obstruction solid or semisolid food brought up into the mouth would not to the same degree interfere with mouth breathing and be distressing in the upright posture during the act of rumination as would milk that fills up the mouth of a baby lying on its back.

In attacking therapeutically the last link in the chain of the motor complex, also the preceding links were being eliminated. The "logic" of this procedure is proven not only by the immediate results of repeated experimental nose obstruction and the eventual therapeutic success in my case, but is evident also to those who keep in mind the similar principle underlying the successful curative administration of bitter pills during meals in some adults, the intense bitterness of the drug in the regurgitated food inducing them to cease not only ruminating but also its first phase, namely, regurgitating.

In merycism in babies, associated with severe pylorospasm or a marked motor insufficiency with stagnation and fermentation or with organic disturbances, such as dilatation of the cardia or the lower part of the esophagus, neither psychic diversion nor nose obstruction will abolish the vomiting or regurgitation (the first and essential phase of merycism); in so far as it depends on these lesions it will still continue. The urgency of the organic component is simply beyond the reach of a psychic influence. Here the therapy naturally must first be aimed at these organic lesions or other anomalies. In the adult ready cures of rumination have repeatedly followed the cure of associated gastro-intestinal diseases.

In connection with the observations as to the rôle the psyche may play in the inhibition of rumination and regurgitation, I wish to submit the following highly interesting observation of a complete cessation of this affection during pertussis and a subsequent cure (from my private practice).

CASE 2.—*History.*—James Q., born Oct. 3, 1917, was a very nervous, irritable, stubborn, but physically well developed boy. Both parents are likewise very nervous and his three sisters had suffered from enuresis nocturna. At the age of 1 year (middle of October, 1918) he suffered from influenza with pneumonia and has often since that time had convulsions, which under bromin therapy became finally less frequent. For a period bromin was discontinued on account of symptoms of intoxication.

In May, 1919, the boy began frequently to "spit up" his food. Whether this was due to large dosages of bromin or not cannot be decided with certainty, as I rarely saw the boy during this period. In August, 1919, I found that he ruminated; the exact beginning of the act could not be determined. After almost every meal, even small ones, the boy would bring up the ingested

food; liquids, such as milk, were borne much better, and if brought up, were reswallowed immediately; semisolid or solid foods were reswallowed after a few masticatory movements.

The rumination was kept up in frequent repetitions and much enjoyed. During some periods conditions would improve, and there was one week when he did not ruminate at all; however, during other periods the trouble would be aggravated and he would ruminate for two or more hours after each meal, even shortly before the next one and practically the whole day during his play with other children. This happened especially during the day previous to an epileptic seizure, when he was very irritable, and during constipation. There was for a long time a very rancid odor to the regurgitated food. Only rarely a real vomiting of any violence occurred; but whenever food would spill over, for instance on the highchair, the boy would put it back into his mouth with his fingers or the spoon and re-eat it despite its rancidity. If scolded he would stop ruminating for a moment, resentfully run away and recommence ruminating.

Treatment.—Various quantitative and qualitative changes of diet, long and short intervals, magnesium, etc., failed to have any noticeable effect. The nervous tension of the home life, through lack of cooperation, rendered pedagogic therapy futile. In April, 1920 the boy contracted pertussis together with the other children of the family. He suffered the most. The paroxysms were very frequent, violent and accompanied by vomiting that continued to the end of May. His general condition, however, was little affected thereby. The remarkable feature was that the boy during this illness had entirely ceased ruminating. Only on May 9 and 19 did he ruminate a very little after breakfast and again in the last week of May and the first week of June. His mother volunteered the remark, "he tried, but did not know how to do it any more." Since that time no more rumination has occurred.

The assumption that rumination should have stopped from lack of stomach contents on account of frequent vomiting is, of course, not tenable, especially in the presence of the fact that the boy's physical condition was good, no signs of underfeeding existing. Most probably it was the mechanical interference with easy and comfortable rumination by the violence of real vomiting and expectoration during the paroxysms, together with his own and his sister's suffering, and the fear of new attacks becoming the center of his attention (as it was so with his worried parents) that crowded out the former neurotic manifestation with the same psychic force as an "event" occasionally has done in adult ruminants. This case is the more noteworthy, since pertussis has been observed to have led to rumination, evidently by the accompanying vomiting.

A similar observation of a curative effect of an intercurrent disease on rumination has been published by Wanietschek.[10] The boy ruminated from the second month of life unceasingly and resisted various treatments, until a temporary cessation took place in his seventh year due to adenectomy. In his eighth year of life a complete and permanent cure occurred in connection with a transitory postdiphtheritic deglutition paralysis. The author ascribes this cure to autosuggestion, maintaining that the boy, much troubled by the disturbance of the

10. Wanietschek: Jahrb. f. Kinderh. **82**:66, 1915.

pharynx (deglutition mechanism), had to avoid the regurgitation of food as much as possible. Schippers observed rumination in two babies to cease temporarily during dyspepsia with meteorism.

That nervous habits may be given up during an illness which is accompanied by malaise, is well known. I have only lately seen in my Cook County Hospital service a 12 months old head roller completely cease this stereotypia during measles. Whether this was permanent, I did not ascertain, as the child left my observation too early, having been transferred to the Contagious Hospital.

A CASE OF ACUTE LEUKEMIA IN AN INFANT *

LAWRENCE WELD SMITH, M.D.

BOSTON

The case of acute leukemia herewith reported, occurring apparently at birth or very shortly thereafter, is, as far as I have been able to discover in the literature, unique in that the patient is the youngest person in whom this disease has been noted. However, Tancré [1] within the past year reported a case in an infant in which the disease began at the age of one month and terminated fatally three months later. Holsclaw [2] also outlines the findings in an acute lymphatic leukemia in a baby, aged 11 months.

The history of the case under discussion was obtained from the family physician, Dr. Marie Knudson, of Boston. It is through her courtesy that the case is being presented.

REPORT OF CASE

The patient is a male baby, 6 weeks of age.

Family History.—The father and mother (both born in Italy) are living and well. Three other children are living and well. The mother has had no miscarriages! There is no known family history of tuberculosis, syphilis, renal or blood disease.

Past History.—The baby was full term and normally delivered. It was breast fed until its present illness. Its birth weight was about nine pounds. There has been no history of infection.

Present Illness.—The baby when about 3 weeks old began to have marked difficulty with its feeding—vomiting most of its food, passing from five to seven loose greenish stools each day, and losing weight. This had been present for about a week and was becoming more severe. The diagnosis of improper feeding with indigestion was made, and its diet regulated by giving alternate feedings of a modified milk formula together with breast milk. The baby did not seem to improve after various attempts to find a satisfactory formula. This led to a more careful physical examination of the baby, and an enlarged axillary lymph node was noted. This lymph node, according to the mother, had been present since birth and had been slowly increasing in size until at nearly 6 weeks of age it had become as large as a walnut. A greatly enlarged spleen was also found at this time. These observations of Dr. Knudson's, in addition to a rather obvious anema, led her to examine the blood and to refer the case to Dr. H. I. Bowditch of the Children's Hospital Staff. Through his kindness I was permitted to see the patient and to report on the blood findings.

1. Tancré, E.: Acute Lymphatic Leukemia in Infants, Arch. f. Kinderh. **67**:7, 1918.

2. Holsclaw, F.: Case of Acute Lymphatic Leukemia, with Autopsy Report, Arch. Pediat. **35**:151 (March) 1918.

Physical Examination.—The baby was a pale, fairly well developed, but poorly nourished infant, about 6 weeks of age, lying in bed, crying fretfully. The child appeared to be ill, was pallid, with a peculiar grayish yellow hue to the skin. The mucous membranes were pale. The sclerae were white, practically bloodless. The pupils were equal and reacted to light. The nose and throat were negative. There were ten or twelve purpuric spots scattered over the body and under the left axilla. These varied in size from a pinhead to about the size of a silver half dollar. The chest was essentially normal in development. The lungs were not abnormal. The heart was not enlarged. There was a loud systolic murmur best heard over the pulmonic area which was considered functional. The abdomen was asymmetrical, protruding prominently on the left side from below and to the right of the umbilicus to the costal margin. On palpation the spleen was felt filling two thirds of the abdomen. There was a prominent notch. The spleen was very firm and had a rounded edge. The liver was slightly enlarged, palpable a finger's breadth below the costal margin. There was a slight enlargement of all the lymph nodes. In the left axilla there was one large discrete nodule, the size of a large walnut, firm and freely movable under the skin. This was apparently not tender and showed no evidence of inflammation. It interfered slightly with adduction of that arm. The reflexes were all normal.

BLOOD EXAMINATION

	Age		
	6 Weeks	7 Weeks	8 Weeks
Leukocytes	189,000	201,000	30,000
Polymorphonuclear leukocytes	1%	2%	2%
Pathologic lymphocytes (large)	22%	18%	32%
Pathologic lymphocytes (small)	69%	72%	63%
Normal small lymphocytes (?)	6%	7%	2%
Large mononuclears (?)	2%	1%	1%
Erythrocytes	2,624,000	1,440,000	900,000
Achromia	+ +	+ +	+ + +
Anisocytosis	+	+ +	+ +
Poikilocytosis	+	+ +	+ +
Polychromatophilia	0	+	+
Stippling	0	0	0
Platelets	Definitely diminished	Definitely diminished	Markedly diminished

Subsequent History.—During the two weeks' period before death that he was under observation, the baby's condition became progressively worse and he continued to lose weight steadily. The spleen became larger, occupying practically the entire abdomen. The axillary lymph node at the time of death was the size of a large hen's egg. Fever developed and remained constantly high. At the age of 2 months, the baby developed a terminal pneumonia and died very suddenly. No necropsy could be obtained, which is regretted, for much of the uncertainty regarding the rather unusual cells found in the blood might have been cleared up by a microscopic examination of the spleen and bone marrow.

The presence of the axillary lymph node from birth suggests a prenatal development of the disease. It is interesting to note in this connection that the mother's blood picture and white cell count was definitely normal.

DISCUSSION

The chief point of interest is the character of the lymphocytes. These cells vary greatly in size and are practically all pathologic cells. A few comparatively normal small lymphocytes occur   Stained by
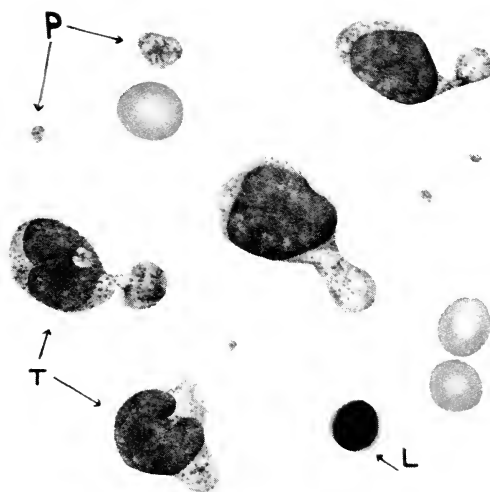
(L) Normal small lymphocyte. (T) Large pathologic lymphoid "tumor"
cells, showing characteristically the intense granulation of both the nuclei and
the cytoplasm and the "budding" of the cytoplasm into long pseudopodia which
break off and can be seen floating free in the peripheral blood stream as (P)
pseudoplatelets which are with difficulty differentiated from normal platelets.

Wright's method all the larger lymphocytes are exceedingly granular in character, their cytoplasm being filled with small, slightly basic staining granules which almost conceal the cytoplasm itself. This is true of the smaller form of cell, also, but is less noticeable. That they belonged to the lymphoid and not the myeloid series was for some time very uncertain, but by using Goodpasture's modification of Graham's oxidase stain, their lymphoid character was definitely determined. This was because the granules failed to be colored by the oxidase stain as they characteristically do in cells of bone marrow origin, except megakaryocytes. These large pathologic lymphoid "tumor" cells resemble somewhat megakaryocytes and though conceivably the cells in this case might be pathologically megakaryocytes, it is believed that such is not the case.

Another feature of these large pathologic lymphoid "tumor" cells is the presence of apparent pseudopods. These can be seen budding from the cytoplasm in many instances, becoming pinched off, and thrown into the blood stream, forming what we may for lack of a better term call "pseudoplatelets." These pseudopodia may be elongated with multiple points of what seem to be division. With Wright's stain these small bits of protoplasm are almost indistinguishable from platelets, for they collect acid staining granules in the center of each process which are in no way associated with the cell nucleus as is shown in the accompanying illustration.

Using the vital staining method with brilliant cresyl blue Minot has noted that "pseudoplatelets" can be distinguished from the typical true platelet, by the absence of the so-called "apron" of the latter. The "pseudoplatelets" as a rule, are much more sharply defined peripherally than are the true platelets, but the staining has to be extremely accurate to show these slight differences. By ordinary fixed staining methods the two are practically indistinguishable, and the appearance of the "pseudoplatelets" tempts one to conceive that possibly the platelets may, under certain abnormal conditions, be formed by other cells than the megakaryocyte of the bone marrow.

These pseudopodia are found almost entirely budding from the larger lymphocytes. They occur in approximately 20 per cent. of these cells and usually as a single process, although they may be multiple with as many as ten or twelve smaller processes. Occasionally, a single "bud" may be pinched off in two or more places. Again, this is unusual. On counting one hundred white cells differentially, usually five or six of these "budding" cells are seen, and approximately a dozen or fifteen of these free circulating "pseudoplatelets."

Dr. George R. Minot, in discussing the blood findings of this patient, commented on the fact that in a much less marked degree,

however, he had noted this "budding" in atypical lymphoid cells, immature large mononuclear cells and endothelial phagocytes present in certain pathologic bloods. From his work with cresyl blue preparations, he too, remarks on the similarity of the true platelet and these "pseudoplatelets."

Such a case as this offers much of speculative interest, but it is not my purpose at this time to do more than record the observations made and to leave the reader to draw his own deductions.

SUMMARY

A case of lymphatic leukemia in an infant is reported. According to the history, the disease began definitely at the age of 3 weeks, while the evidence seems to suggest strongly an intrauterine development of the condition.

The lymphocytes are nearly all of a pathologic type. They show an excessive granulation of the cytoplasm, making a differential diagnosis from myelogenous leukemia extremely difficult. They further show to a marked degree another unusual feature, namely, a budding of the protoplasm. Some of these buds become detached and circulate in the blood. They very closely resemble normal true platelets.

BROMIN POISONING THROUGH MOTHER'S MILK *

FRANK VAN DER BOGERT, M.D.
SCHENECTADY, N. Y.

REPORT OF CASE

History.—A 6 months old nursing baby was referred to Dr. Hartman of Alexandria Bay to the pediatric department of the diagnostic clinic of the state department of health at Carthage, N. Y., Oct. 1, 1920.

The infant presented a seemingly painful papulopustular eruption, the lesions being grouped and each group surrounded by a clear cut inflammatory area. The lesions were distributed principally on the arms, lower legs and buttocks, and were just beginning to show on the face and scalp. Several patches had assumed a more red or purplish-red color, had reached a papillomatous or condylomatous condition and covered much skin surface, one on the lower leg being at least one square inch in area. There was a history of a general "white" rash at birth, followed by the present eruption at 6 weeks of age. A marked rattle had been heard in the throat, dating from soon after birth, but there was no history of "snuffles." Some irritation of the nasolabial fold was noted at the time of examination.

Family History.—The mother is exceedingly nervous, and for this condition has been taking for the past two years a proprietary remedy known as Miles' Restorative Nervine. The 1912 report of the Massachusetts Board of Health describes this preparation as bromids in sugar syrup with benzoic acid— a heavy syrup containing about 17 per cent. bromids, chiefly potassium and sodium, with a smaller amount of ammonium bromid and a small amount of benzoic acid. The analysis made by the American Medical Association, reported Sept. 9, 1916, is as follows:

MILES' RESTORATIVE NERVINE

	Per Cent.
Ammonium bromid	1.13
Potassium bromid	9.87
Sodium bromid	6.93
Sodium chlorid	0.24
Benzoic soda, etc.	

The baby had been given no medication until two days before appearance at the clinic, when some small sedative tablets were prescribed by the attending physician.

Diagnosis.—The diagnosis of bromid eruption was made by Dr. Edward H. Marsh, dermatologist in attendance, before the history of the mother's medication had been obtained. A specimen of the breast milk was secured later, and an analysis by Prof. Edward Ellery of the department of chemistry of Union College showed it to contain bromin in more than traces. The small amount of breast milk obtainable was probably responsible for the small amount of bromin demonstrated.

COMMENT

Instances of the elimination of drugs through the milk of the nursing mother occur in literature. Holt [1] says that the elimination

---

1. Holt, L. E.: Diseases of Infancy and Childhood, Philadelphia, D. Appleton & Company, 1916, p. 143.

of drugs through the milk is somewhat uncertain and variable. "Few of those popularly supposed to affect the child through the milk really do so." He says that belladonna given in full doses regularly appears in the milk, that the iodids and bromids when long administered may be eliminated in sufficient quantity to produce their constitutional effects on the child.

Dunn [2] believes that the fact that certain drugs taken by the mother can be excreted by the milk has been definitely proven and quotes Talbot, in whose list bromid appears. He says, however, that these drugs are found in the milk only in slight traces and can probably do no harm, except in the case of salvarsan, when sudden death of the infant has occurred after treatment of the mother.

Chapin and Pisek [3] advise that great care be exercised in giving drugs to nursing women, as they may be excreted in the milk. They do not specifically mention the bromids.

Budin [4] apparently does not mention drugs but reports a case of convulsions in an infant suckling a mother who was taking large quantities of alcoholic beverages. The patient was quickly cured when a wetnurse was substituted.

Louis Fischer [5] includes bromids in his list, and states that physiologic experiments have frequently demonstrated the fact that many drugs can be given to the infant through the milk.

Still [6] warns that a possibility always to be remembered where the breast milk appears to be disagreeing with an infant is that the mother may be taking some drug which is either excreted in the milk or affects the milk indirectly.

Koplik [7] mentions only iodin, salicylic acid and atropin as being eliminated in the milk, but says very little is actually known as to the appearance of drugs.

Grulee [8] believes that, in general, one may say that in physiologic doses very few drugs pass over into the breast milk, while in poisonous doses most of them do.

According to Griffith [9] bromin passes into the milk to some extent and occasionally in a way to affect the infant seriously.

2. Dunn, C. H.: Pediatrics 1:249, 1917.

3. Chapin and Pisek: Diseases of Infancy and Childhood, New York, William Wood & Co., 1913, p. 122.

4. Budin, P.: The Nursling, 1907, p. 93.

5. Fischer, L.: Diseases of Infancy and Childhood, 1914, p. 88.

6. Still, G. F.: Common Disorders and Diseases of Childhood, London, Oxford University Press, 1910, p. 26.

7. Koplik, H.: The Diseases of Infancy and Childhood, Philadelphia, J. B. Lippincott Company, 1910, p. 97.

8. Grulee, C. G.: Infant Feeding, Philadelphia, W. B. Saunders Company, 1914, p. 79.

9. Griffith, J. P. C.: The Diseases of Infants and Children, 1919, p. 106.

Lowenburg [10] does not mention bromids.

I have been unable to find a specific instance relating to the bromids, although Talbot [11] refers to Burcura as his authority. This reference I have not obtained.

Reed [12] has collected a large number of cases in which nursing babies have been apparently affected by drugs administered to the mother. He refers to Rosenhaupt, who used potassium and sodium bromid in an epileptic woman, and was able to demonstrate chemically that the bromin passed over into the milk. He does not consider this dangerous, however, nor especially to be avoided, since only an infinitesimal amount passes over. He says that the transmission of medical substances through the milk of the mother to the babe is a subject of more than usual obscurity, and that owing to the prevalence of tradition and the absence of thorough and accurate methods in collecting the data, the observations are for the most part valueless.

CONCLUSION

In conclusion, it might be added that the papillomatous or condylomaform areas are described by Stelwagon [13] as a rather rare manifestation occurring especially in children and adolescents, and that, especially in children, the eruption may persist for several weeks after the drug has been discontinued. This is apparently more apt to occur in the condylomaform type.

Fox [14] speaks of the treatment of drug eruption as a simple matter, but excepts a few cases of bromid eruptions which do not disappear speedily.

10. Lowenburg, H.: Infant Feeding and Allied Topics, Philadelphia, F. A. Davis Company, 1916, p. 43.

11. Morse and Talbot: Diseases of Nutrition and Infant Feeding, New York, The Macmillan Company, 1915, p. 114.

12. Reed, C. B.: Surg., Gynec. & Obst. **6**:514, 1908.

13. Stelwagon, H. W.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1902, p. 424.

14. Fox, H. F.: Atlas of Diseases of the Skin **1**:59, 1905.

A STUDY OF SEVENTY-THREE CASES OF ACUTE ARTHRITIS IN INFANTS *

F. ELMER JOHNSON, M.D.
NEW YORK

The invasion of the joints and periarticular tissues by pyogenic organisms in infants is by no means a rare condition. The inflammation of the joint is usually secondary to an infection of the epiphysis. However, in many instances the inflammation spreads from the epiphysis to the periarticular tissues without affecting the joints proper. Clinically, there is great swelling, with or without suppuration, tenderness, redness and a great amount of induration.

This paper is a statistical study of seventy-three consecutive cases admitted to the Babies Hospital in the past fifteen years. The common conception seems to be, that purulent arthritis always follows a focal lesion. This may be true, but the focus of infection is indeterminable in the majority of instances. Of the seventy-three patients reported in this study, only thirty-two gave a history or showed on examination when admitted, any definite source of infection. Many are included in this number who had had pneumonia or some other acute illness several weeks previously and the relation between the original infection and the arthritis is not at all clear. For instance, following a pneumonia, an infant may develop a streptococcic arthritis.

Table 1 gives the possible sources of infection in these thirty-two infants.

To illustrate the difficulties in drawing conclusions as to the possible source of infection, the ten cases preceded by pneumonia were analyzed. Only three of these showed pneumococci in the pus aspirated from the lesions; one showed the gonococcus, one the aurococcus and one the influenza bacillus while four failed to show any bacteria in the aspirated material.

The number of males seems to predominate. There were forty-six boys and twenty-seven girls. This difference may, in part, be due to the large number of girls rejected on admission on account of positive vaginal smears. The rule in the hospital has always been to reject all children suspected of having any gonococcic infection of the genitals. However, the greater number of boys affected would seem to indicate that vaginitis is not as common a cause of arthritis in infants as is usually supposed.

The ages of these infants is an interesting study.

TABLE 1.—Sources of Infection

Infection	No. of Cases
Pneumonia	10
Navel infection	4
Furunculosis	3
Cerebralspinal meningitis	2
Cervical adenitis	2
Vaginitis	2
Ophthalmia	2
Infected wounds	2
Otitis media	1
Scarlet fever	1
Breast abscess in mother	1

TABLE 2.—Ages of Patients

Age	Number of Cases
0 to 1 month	12
1 to 2 months	4
2 to 3 months	9
3 to 4 months	3
4 to 5 months	8
5 to 6 months	3
	39
6 to 7 months	6
7 to 8 months	5
8 to 9 months	4
9 to 12 months	0
	15
12 to 15 months	7
15 to 18 months	4
	11
18 to 21 months	4
21 to 24 months	0
24 to 30 months	1
30 to 36 months	1
36 months	2

TABLE 3.—Order of Frequency in which Joints were Affected

Joint	Number
Knee	27
Ankle	26
Wrist	25
Shoulder	24
Hip	17
Elbow	14
Metacarpophalangeal	12
Thumb	3
Interphalangeal	9
Hand	8
Foot	1
Sternoclavicular	6
Metatarsophalangeal	5
Great toe	3
Temporomandibular	2
Intercarpal	2
Carpometacarpal	1
Tarsometatarsal	1
Intertarsal	1

TABLE 4.—MICROORGANISMS CAUSING THE INFECTION

Streptococcus	18 cases
Pneumococcus	14 cases
Gonococcus	7 cases
Staphylococcus	3 cases
Influenza	3 cases
Colon bacillus	1 case
Meningococcus	1 case

TABLE 5.—RELATIONSHIP BETWEEN ORGANISM AND NUMBER OF JOINTS INFECTED

Organism	Number of Cases
Streptococcus affected one joint in	4 cases
Streptococcus affected two joints in	2 cases
Streptococcus affected three or more in	12 cases
Pneumococcus affected one joint in	9 cases
Pneumococcus affected two joints in	4 cases
Pneumococcus affected three or more in	1 case
Gonococcus affected one joint in	1 case
Gonococcus affected two joints in	1 case
Gonococcus affected three or more in	5 cases
Influenza bacillus affected one joint in	2 cases
Influenza bacillus affected two joints in	0 cases
Influenza bacillus affected three or more in	1 case
Staphylococcus affected one joint in	1 case
Staphylococcus affected two joints in	1 case
Staphylococcus affected three or more in	1 case

TABLE 6.—NUMBER OF JOINTS INVOLVED IN INDIVIDUAL CASES AND CAUSATIVE ORGANISM

Number of Joints Affected	Number of Cases	Organism
8	1	Gonococcus
7	1	Streptococcus
6	2	1 Streptococcus 1 Pneumococcus
5	4	2 Streptococcus 2 Gonococcus
4	4	3 Streptococcus 1 Gonococcus
3	8	5 Streptococcus 1 Gonococcus 1 Influenza

TABLE 7.—RESULTS OF BLOOD CULTURE STUDIES

Blood Cultures	Organisms of Joints					None
	Streptococcus	Gonococcus	Staphylococcus	Influenza Bacillus	Pneumococcus	
10 negative	0	1	1	0	4	4
9 positive	4	0	0	1	2	2

TABLE 8.—CAUSES OF DEATH

Diseases	Cases
Bronchopneumonia	15
Marasmus	13
Erysipelas	5
Meningitis	4
Peritonitis	2

If the number of babies are arranged in six month periods, the result is striking in showing that the younger the infant, the greater seems to be his susceptibility to purulent arthritis. Fifty-three per cent. of all the babies in the study were under 6 months of age, and 74 per cent. were under 1 year. The twelve babies who were one month or under, were probably victims of birth infection. This, however, is difficult to substantiate for only four infants presented definite signs of ophthalmitis on admission. Other routes of infection than the cord are responsible. It is possible that bacteria enter the blood stream through injuries to the mucous membranes of the mouth or to trauma from forceps.

Forty-two per cent. of the children had only one joint affected; 25 per cent. had two joints affected while 33 per cent. had more than two joints affected. The largest number of joints affected in any one case was eight. In Table 3 the joints affected are arranged according to frequency.

Table 3 also shows 95½ per cent. of the joints affected were in the extremities.

In forty-seven babies the organism responsible for the infection was isolated and identified by culture. Table 4 shows that the principal organisms were the streptococcus and the pneumococcus.

To ascertain whether an organism is more prone to attack one or more joints, Table 5 was compiled.

It would seem that the streptococcus and gonococcus are much more prone to affect multiple joints while the pneumococcus seems to be limited more often to one or two joints. This bears out the usual impressions.

From the sterno-clavicular joint the streptococcus was isolated in two children, the gonococcus in two and the influenza bacillus in one child. Gonococcus and streptococcus were found in one case in which the temporomandibular joint was affected. One baby had eight joints affected in the course of the disease. This was the largest number in any one child in the series and the gonococcus was responsible. Another child had seven joints affected in which the streptococcus was isolated from all.

During the past two years blood cultures have been made routinely in all cases of arthritis. There have been nineteen children in whom one or more blood cultures have been taken. In ten, the culture proved sterile. Of the nine who showed a positive growth, four proved to have streptococcus, three pneumococcus, one the influenza bacillus and one staphylococcus.

Two children had positive blood cultures but showed no organisms from the joints. One had a positive culture of staphylococcus and the other a mixed infection of pneumococcus and meningococcus. All

the children who had a streptococcus in the joints had also a positive blood culture for the same organism. Forty per cent. of the negative blood cultures were in children who showed no organisms in the joints while in the positive cultures only 22 per cent. had no organisms in the lesions. In other words, when organisms are found in the joints there is more apt to be a positive blood culture. In no case was a different organism found in the blood than was isolated from the arthritic lesion. The series seems too small, however, to draw any very definite conclusions.

The prognosis is not very hopeful among infants with this disease. Fifty-three per cent. died in the hospital and 9 per cent. were discharged unimproved, which usually means that the children were taken out of the hospital against the advice of the physicians. Thirty-eight per cent. were followed and reported entirely well or greatly improved.

Table 9 gives the number of children and the mortality in each age group.

TABLE 9.—Mortality of Various Age Groups

Age	Number of Cases	Died	Mortality Percentage
1 to 6 months	39	25	64.1
6 to 12 months	15	8	53.3
12 to 18 months	11	4	36.2
18 to 24 months	4	1	20.0
24 to 30 months	1	1	100.0
30 to 36 months	1	0	
36 months	2	0	

Five children of this series have recently been seen, 2 eleven years, 1 eight years, 1 six years and 1 four years after discharge from the hospital. The functional result in all is perfect. One child when admitted to the hospital in 1911, at 5 months of age, was suffering from a severe infection of the right hip. Three large incisions were made with drains inserted through and through from beneath Poupart's ligament to the gluteal region. The infecting organism was the streptococcus. The result was perfect, except for a very slight limp. The thigh can be moved normally in every direction. There is no appreciable difference in the length of the extremities. Very few of these children died from the disease itself. In the cases that came to necropsy, evidence of some other disease sufficient to cause death was found. The other children either died from diseases determined clinically or from slow wasting. The causes of death recorded in the histories are shown in Table 8.

As would be expected, four of the children who died of erysipelas were infected in their joints with streptococcus.

In one of the children with meningitis, the influenza bacillus was recovered from the joints and spinal fluid. Another child had the influenza bacillus in the spinal fluid, blood and joints. A third child had streptococcus in blood, spinal fluid and joints. The fourth died suddenly and unfortunately no examination is recorded of the spinal fluid. The material aspirated from the baby's joints was sterile.

The prognosis is affected materially by the age. The older the baby, the better chance he has to recover. The high mortality among young babies is due in great part to the difficulty of feeding.

I am indebted to Dr. L. Emmett Holt, physician in chief to the Babies' Hospital, for the privilege to report these records.

DEVIATION OF THE AORTIC SEPTUM: COMPLETE TRANSPOSITION OF THE GREAT VESSELS, WITH REPORT OF TWO CASES IN INFANTS *

VICTOR C. JACOBSON, M.D.

Resident Pathologist of the Peter Bent Brigham Hospital

BOSTON

Congenital cardiac abnormalities are encountered sufficiently often to emphasize the manifold possibilities of such defective development, their frequent multiplicity of expression in a single case, and the difficulties in the way of recognizing antemortem the actual lesions present. Such signs as cyanosis since birth, a loud murmur and thrill at the base of the heart, and clubbed fingers—when taken together are quite pathognomonic of congenital heart disease. But defects of the organ acquired in utero are seldom single, and the mechanical explanation of the physical findings is often a difficult problem.

Complete transposition of the great vessels is uncommon enough to warrant publication of such cases as are proved at necropsy. I have found two instances of this condition in infants, one living three weeks and the other twelve months, the duration of life and the relation of the heart lesions thereto furnishing an instructive feature. The cases are from the clinic of Dr. Chas. Hunter Dunn at the Infant's Hospital, Boston, and I am indebted to him for the clinical data.

REPORT OF CASES

CASE 1.—Male, white, aged 12 months.

Family History.—Father and mother are living and well. There is no history of miscarriages, tuberculosis or syphilis.

Past History.—Born at full term, normal delivery, weighing 5½ pounds. Cried normally but was blue. He has had an occasional cold.

Present Illness.—Baby has been blue since birth, especially when he cries. He is sent in with a diagnosis of congenital heart disease and for regulation of his feeding.

Physical Examination. — Baby is cyanotic, more so on crying. Anterior fontanel admits two fingers. Craniotabes present. There is right interscapular dulness and spinal dulness to the level of the fourth vertebra. Heart: There is a palpable thrill and diffuse impulse over the precordium. Enlargement is made out 2 cm. outside the left nipple line, and 3 cm. from the midsternal line to the right. A systolic murmur is heard at the apex and faintly in the vessels of the neck

A week later the following note was made: "There is still marked cyanosis which is increased by crying. The cardiac impulse is diffuse and there is a

---

palpable thrill. The heart borders are unchanged. A loud systolic murmur is heard all over the precordium, transmitted into the left axilla and back but not into the vessels of the neck."

Diagnosis.—Pulmonic stenosis and patent interventricular septum.

Pulse rate varied between 135 and 170 per minute and respirations from 37 to 78. The following week he developed a fever and chest signs of bronchopneumonia and died.

Necropsy Diagnoses.—Complete transposition of aorta and pulmonary artery; patent foramen ovale; patent interventricular septum; vegetative endocarditis of the wall of the septum defect; vegetative endocarditis of the tricuspid valve with insufficiency; right auricular and ventricular hypertrophy; passive congestion of the lungs.

Fig. 1.—Case 1. Heart, anterior aspect. 1. Aorta. 2. Pulmonary artery. 3. Ductus arteriosus.

Body is that of a somewhat emaciated male white infant, 60 cm. in length. There is slight postmortem lividity. The primary teeth are present. There are no external stigmata and no clubbing of the fingers.

Peritoneal Cavity: The abdominal viscera are in normal positions. The urachus is closed.

Pleural Cavity: Contains no free fluid.

Mediastinum: The thymus is small and of loose texture, weighing about 4 gm. The greater part of the mediastinum is occupied by the enlarged heart which lies in about normal position.

Pericardial Cavity: Contains about 10 c.c. of clear fluid.

Heart: Weight, 76 gm.; diameters, 8.5 by 7 cm. Several abnormalities are apparent on opening the pericardium. It is considerably enlarged, the right

auricle markedly dilated and placed rather posteriorly. The general contour of the organ follows about normal lines, although the anteroposterior diameter is probably increased out of proportion to the general hypertrophy. Viewed anteriorly, the most conspicuous anomaly is the origin of the aorta, this vessel arising from the conus arteriosus of the right ventricle a little to the right of the usual origin of the pulmonary artery.

The pulmonary artery has its origin in the left ventricle, whence it arises to the left of and slightly posteriorly to the aorta, the greater part of the arch of which is in close apposition to the convexity of the pulmonary artery. The left auricle is small and empty, but its appendage is rather elongated, extending about 0.5 cm. along the anterior longitudinal sulcus.

The superior and inferior venae cavae enter the dilated right auricle, their ostia being 1 cm. apart, and that of the inferior vessel being high up on the posterior wall.

The aorta is 1.3 cm. in diameter at its base. It gives off two main coronary branches, the right and left, the left making its exit in plain view anterior to the pulmonary artery, passing under the left auricular appendage where it gives off its auricular and anterior circumflex branches. From the aorta arise in a normal manner the innominate, left common carotid and left subclavian arteries. The ductus arteriosus is 1 by 0.3 cm. and connects the pulmonary artery at a point on the upper anterior wall just proximal to its primary division, to the aorta just below the origin of the left subclavian artery. It is entirely closed by an endarteritis.

The incision through the tricuspid valve and lateral wall of the right ventricle encounters a greatly hypertrophied myocardium. That of the right auricle is hypertrophied in proportion. The foramen ovale is widely open, the patency being 1.2 cm. in diameter, practically round in outline and bordered by a rather high limbus. The tricuspid valve leaflets are nodular and thickened, pale ragged vegetations covering the free borders and producing sufficient puckering to cause a high degree of insufficiency. The circumference of the valve orifice is 4.7 cm. The chordae tendineae are taut and the papillary muscles greatly hypertrophied.

In the membranous portion of the interventricular septum is a defect 0.8 cm. wide and rounded in outline. The greater part is occluded by a mass of cauliflower-like granulations so that an actual opening of only 0.8 cm. exists along the lower border.

The left auricle is small and its wall is only 0.1 cm. thick (after fixation). The mitral valve is normal. The left ventricle wall is only 0.4 cm. thick. From the left ventricle 1 cm. above and to the left of the interventricular septum defect the pulmonary artery arises. It gives off in an essentially normal manner the right and left pulmonary branches. The position of the ductus arteriosus has been described. The main pulmonary artery is 0.8 cm. in diameter just above its valve and there is no evidence of stenosis.

The lesions in this heart consist, therefore, of complete transposition of aorta and pulmonary artery, with reversal of the usual muscular preponderance of the two ventricles. The right auricle is markedly dilated and hypertrophied. The large patent foramen ovale makes virtually a single chamber of the auricles. The interventricular septum defect is practically closed by granulations so that the minute opening still present is probably of little consequence.

Lungs: Weight of right, 52 gm.; left, 38 gm. The posterior two-thirds of each lung are similar in appearance, being dark red on the pleural surface and boggy. The anterior portions are pink and crepitant. On section, from the anterior portions exudes a pale frothy fluid and from the posterior a bloody, frothy fluid. The alveolar outlines are as a whole quite distinct. The trachea and primary bronchi are normal.

Spleen: Weight, 14 gm. It presents the appearance of chronic passive congestion.

Gastro-Intestinal Tract: Appears normal

Pancreas: Appears normal.

Liver: Weight, 186 gm. It is dark red with a smooth capsular surface. On section much dark red blood escapes from the hepatic veins. The lobules are indistinctly outlined by pale red lines.

Gallbladder, Kidneys, Suprarenals and Bladder: Appear normal.

Aorta: Shows no abnormality in its branching.

Case 2.—Male, white, aged 3 weeks.

Family History. — Father and mother well. There is no history of miscarriages.

Past History.—He is the second baby and of normal birth. There have been no convulsions nor disturbance of feeding. The baby is brought to the hospital because of marked cyanosis and with the diagnosis of a "bad heart."
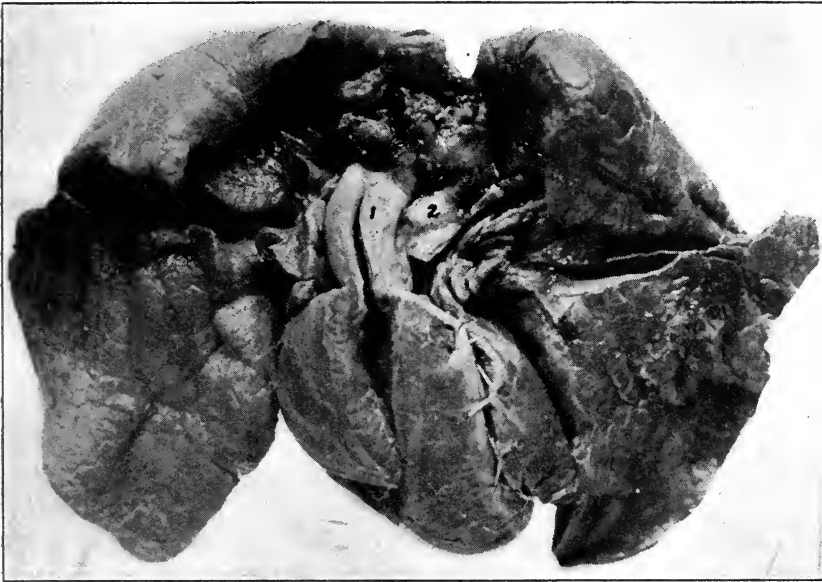
Fig. 2.—Case 2. Heart and lungs, anterior aspect. 1. Aorta. 2. Pulmonary artery. 3. Ductus arteriosus.

Physical Examination.—Baby has marked cyanosis, more especially over the face and becoming worse with crying. There is moderate dyspnea. The lungs are fairly clear throughout. Over the heart a systolic murmur is heard at the base at the junction of the second rib and sternum on the left.

Diagnosis.—Pulmonic stenosis (?). Malformation of the vessels. Roentgen-Ray Report: Slight enlargement of the heart to the left. The right hilus is suggestive of atelectasis. Pulse rate varied between 140 and 150 per minute; respirations from 40 to 60. Death occurred twenty-three days after entrance.

Necropsy Diagnoses.—Complete transposition of aorta and pulmonary artery; patent ductus arteriosus; slightly patent foramen ovale; congestion of thoracic and abdominal viscera: mongolian facies; accessory spleens.

Body is that of a fairly well nourished male, white infant, 50 cm. in length. There are no external stigmata except for slight mongolian aspect of the eyes and some outward bowing of the legs with slightly enlarged epiphyses. The anterior fontanel is open 2 cm. and somewhat depressed.

Peritoneal Cavity: There are no adhesions or free fluid. The organs are in normal positions. The diaphragm on both sides is level with the fourth rib. Pleural and Pericardial Cavities: Contain no excess of fluid.

Heart: As it lies in situ it appears rather larger than normal in every respect. The left side is soft and collapsed, altering the usual rounded outline of this part of the organ. The ascending aorta is prominent, completely covering from view the pulmonary artery and externally apparently coming off from the right side of the heart. The heart, empty, measures 4.8 by 4.2 cm. There is marked hypertrophy of the myocardium of the right ventricle, the wall being 1.7 cm. in thickness, the left ventricle 0.3 cm. The valves are smooth and glistening and there are no signs of stenosis. The ventricles contain a scant amount of fluid blood. The auricular appendages are empty. There is complete transposition of the great vessels, the aorta coming from the right ventricle immediately to the right of the interventricular septum and the pulmonary artery from the left ventricle, about 0.5 cm. to the left of the septum. The superior and inferior venae cavae enter the right auricle and the pulmonary veins enter the left auricle in a normal manner. There is a patulous ductus arteriosus which measures 1.5 cm. in length with a lumen of 3 mm. extending between the pulmonary artery and the aorta which it joins just beyond the level of the innominate artery. The foramen ovale has a narrow crescentic opening along the lower border, fairly well covered by the limbus. The interventricular septum is entirely closed.

Lungs: Were removed with the heart. They are of a pale, grayish red color, give crepitation and on section the bronchi show some yellowish, frothy fluid escaping. The trachea and bronchi are normal.

Spleen: Weight, 15 gm. It is very dark red and the surface is tense. The pulp is markedly congested. There are two accessory spleens close to the hilum, measuring 2 and 3 mm. in size, respectively.

Gastro-Intestinal Tract: Shows considerable edema and congestion throughout.

Liver: Weighs 98 gm. and is markedly congested.

Kidneys: Weigh 12 gm. each. The fetal lobulations are still conspicuous. The cortex and medulla are moderately congested.

Aorta: There is no abnormality in the size or branching.

DISCUSSION

The developmental errors which result in complete transposition of the aorta and pulmonary artery are chiefly two, according to Rokitansky,[1] who gave the first reasonable explanation for the phenomenon. These are: (a) a deviation of the aortic septum within the truncus aorticus, and (b) its faulty union with the interventricular septum.

Early in fetal life the elongated truncus aorticus is divided into aorta and pulmonary artery by a process in which three factors each play a part. These are, first, a proximal and, second, a distal part of the endocardial swellings in the bulbar part of the truncus aorticus which are known as the proximal and distal bulbar swellings and, third, the aortopulmonary septum. These three elements, at first distinct, later blend to form the spiral septum with its concavity facing posteriorly and to the right, dividing the truncus aorticus into aorta and pulmonary artery. With the ventricles in their normal position any deviation of the septum will cause a change in the relative positions of

1. Rokitansky: Defekte der Scheidewande des Herzens, Vienna, 1875.

the two vessels and transposition will result, the aorta arising from the right ventricle and the pulmonary artery from the left ventricle.

The part played by faulty union of the aortic septum with the interventricular septum may be very important. Quoting from Abbott [2] " . . . in the normal heart, in the union of the aortic and interventricular septa, the latter becomes continuous with the left wall of the aorta in front and with its right wall behind (through the pars membranacea), surrounding the vessel on its right side in such a way that the latter becomes placed in the left ventricle, while the pulmonary artery comes to lie in the right. Should this union take place at an abnormal angle, so that the interventricular septum surrounds the vessels rising posteriorly, on its left instead of its right wall, the trunks will be placed in the reversed cavities and again, even though the trunks may be in a normal relation to each other, transposition will ensue."

Complete transposition is incompatible with long life. Emanuel's patient,[3] who lived eleven years, is the oldest case on record; most patients varied in age from a few days to several months. The maintaining of the pulmonary circulation is of greatest importance, and some means must be provided for supplying oxygenated blood to the aorta. The fetus requires no special mechanism, as the pulmonary circulation has not been established. If in an infant with complete transposition immediately after birth the foramen ovale and ductus arteriosus become closed as normally occurs, then the aorta would be supplied with venous blood from the right ventricle and the pulmonary circulation through the left side of the heart and lungs would be a closed circuit. However, cardiac anomalies are seldom single, particularly in the major errors and some means which, nevertheless, is almost always insufficient is provided for passage of oxygenated blood from the pulmonary system to the aorta.

The usual accessories are a patent foramen ovale, a patent ductus arteriosus, a perforate interventricular septum or combination of these. With a widely open foramen ovale blood from the lungs can pass back into the right auricle to escape into the aorta through the right ventricle. Case 1 had such a channel and lived a year even with a patent interventricular septum closed by granulations. An open ductus arteriosus is probably seldom of sufficient caliber to compensate as well as a fully open foramen ovale and Case 2 with a very slight aperture for a foramen and a patent ductus with a caliber of about 3 mm. was insufficient to supply oxygenated blood to the systemic arterial circulation, the patient living but six weeks.

---

2. Abbott: Osler's Modern Medicine **4**:368.
3. Emanuel: Reference in Abbott's Article, Osler's Modern Medicine **4**:368.

In Case 1 there was also an acquired tricuspid insufficiency. With this additional lesion the mechanics of the circulation might be explained as follows: During right auricular systole, blood would be propelled both through the tricuspid valve and through the foramen ovale. However, at systole of the left auricle there would tend to be a current through the foramen from left to right. This blood would be oxygenated and be mixed with the venous blood of the right auricle but likely not in equal proportions on account of the muscular preponderance of the right side of the heart and the regurgitation through the tricuspid valve. These two factors would produce a pressure in the right auricle greater than that in the left and a mixture of blood from the two sides made difficult. Consequently, there would tend to be an anoxemia in the systemic circulation and it is thus seen that the tricuspid insufficiency undoubtedly was an important contributory factor in the death of the patient.

In Case 2 there was a foramen ovale of very small proportions, too small to give any symptoms in an otherwise normal heart. The ductus arteriosus was open but its lumen was too small to compensate for the abnormal origin of the great vessels. The life of the child was consequently of short duration, six weeks, in striking contrast to the first child with a widely patent foramen ovale and who lived a year.

THE RESISTANCE TO ACUTE DISEASE OF THE RESPIRATORY TRACT IN CHILDREN *

JOHN ZAHORSKY, M.D.

ST. LOUIS

In another article [1] I referred to the relative immunity which develops in children from the seventh to the ninth year. While this conception is common among physicians, I do not know of any study which shows this in plain figures.

I have gone over my records for six years (1913-1918) and tabulated the age of the children who were seen suffering from acute disorder of the respiratory tract. This series embraced the following diseases: Coryza, adenoiditis, otitis media, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis, bronchiolitis, bronchopneumonia and pneumonia; cases of grippe, colds and coughs were also included. Cases of Spanish influenza occurring during the epidemic of 1918-1919, were excluded.

It should be remembered, however, that this does not include all the cases occurring in families. Many mild cases and so many "colds" in older children do not produce sufficient anxiety to the parent so that a physician's advice is sought. The curve, then, represents the age incidence of respiratory diseases, the symptoms of which were sufficiently intense to cause the parent apprehension. The milder reactions of the respiratory tract are generally called "colds" and are treated by home remedies.

DATA AS TO AGE, BASED ON 2,896 CASES

Age	Cases
From 0 to 1 year	503
From 1 to 2 years	393
From 2 to 3 years	318
From 3 to 4 years	285
From 4 to 5 years	302
From 5 to 6 years	357
From 6 to 7 years	277
From 7 to 8 years	172
From 8 to 9 years	93
From 9 to 10 years	65
From 10 to 11 years	47
From 11 to 12 years	35
From 12 to 13 years	29
From 13 to 14 years	20

These figures are plotted in a curve. A study of this curve shows, first, the precipitous decline of the incidence of acute respiratory dis-. eases after the seventh year. It corroborates the popular belief that the body changes at the seventh year. While "colds" still occur, they are less severe and less frequent.

The extremely high incidence in infancy, which this curve shows, must be modified by the well known fact that parents are prone to send for a physician for trifling ailments in infants; also that infants react more severely to respiratory infections. It is extremely doubtful whether disease of the respiratory system is more frequent at 1 year than at 3 years.

A curious phenomenon is found in the sudden elevation at the fifth and sixth year. This corresponds to the beginning of school life.

Age	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14
No Cases														
500														
400														
300														
200														
100														
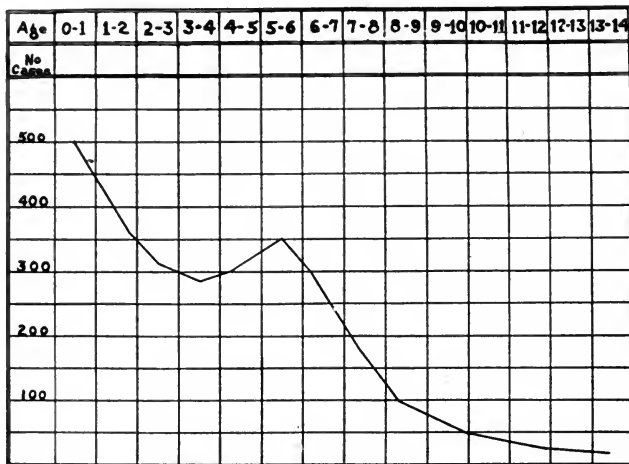
An analysis of a large number of these cases at this age demonstrates that two factors are operative: (1) the extreme susceptibility of many children who have not been exposed to a variety of respiratory infec- tions until they enter school; (2) the frequent repetition of respiratory disease in some children at this age (recurrent tonsillitis, recurrent bronchitis).

It is clear from this study that most persons develop a relative immunity to respiratory infections in early childhood. This immunity is acquired gradually but is subject to many fluctuations in severity during the process of development. Several mild attacks may be followed by a severe attack; or one or more local diseases with no general reaction may precede a serious disease with marked constitu- tional symptoms. Nevertheless, taking a large number of children, this gradual increase in the resistance may be plainly discerned.

I distinguish three stages in the development of this resistance: (1) infantile resistance, (2) puerile resistance and (3) normal resistance:

The infantile resistance to respiratory infections, as its name implies, is found mostly in infants. It is characterized by several features. The infant is less able to resist the morbific agents and the disease spreads throughout the respiratory tract. The coryza nearly always terminates in a bronchitis or bronchopneumonia. Hence, an extensive invasion of the respiratory tract is the most marked peculiarity of infantile resistance.

Another distinctive character is the presence of general symptoms. Fever, prostration, restlessness, anorexia and loss of weight are generally present in infants even when the pathogenic agent is slightly virulent, as in the common cold. Then, there is the development of adenopathy, which becomes most marked when the infectious agent is very virulent. Then suppuration is frequent. The great tendency to otitis media and bronchopneumonia is characteristic of the infantile resistance. The duration of the disease also is longer than in the older child.

Puerile resistance is characterized by an invasion of only a part of the respiratory tract and a fleeting appearance of general symptoms. The disease tends to remain localized but the febrile reaction may still be great; the duration, however, is short. Adenopathy, except tonsillitis, is uncommon and otitis media and bronchopneumonia become less frequent.

A normal resistance is shown when there is only a localized reaction and no febrile disturbance. A coryza, a pharyngitis, laryngitis, or tracheitis may develop, but except for a few days' lassitude and the annoyance of the local symptoms, the patient is not sick.

These different stages of resistance are not limited to the ages indicated by the curve of incidence. Thus, a child may persistently show an infantile resistance throughout the whole period of childhood. These children are well known to pediatrists. Every time the grippe occurs in a family, the susceptible child shows a serious bronchitis or bronchopneumonia. On the other hand, the baby may be born with a normal resistance, that is, he never acquires anything more severe than a common "cold." Then, again, the child may show a normal resistance until he enters school and for many months an infantile or puerile resistance is manifested. An acute infectious disease, such as whooping cough, measles, etc., may alter the resistance for months. A chronic infected focus—tonsil, tooth or gland—often changes the type of resistance.

The value of having some clinical standards whereby we gage the resistance of an infectious disease is unquestionable. Whether the suggestion that we distinguish three grades of resistance is really useful remains to be seen. However, there is a great difference in children in their resistance to the respiratory infections, and since we must depend in the prophylaxis and cure of these common diseases almost entirely on this resistance, every little effort to elucidate the subject will be serviceable.

THE DIAGNOSIS AND PROGNOSIS OF TUBERCULOSIS IN INFANCY *

CHARLES HUNTER DUNN, M.D.

AND

SAMUEL A. COHEN, M.D.

BOSTON

In 1914, under the stimulus of the ability to examine postmortem material in a large percentage of fatal cases at the Infants' Hospital, we began a detailed study of tuberculosis in the first two years of life. This study while, perhaps, not disclosing anything very startlingly new, has given results which may be of value in emphasizing certain peculiarities of the disease at this period of life, and which have the advantage of being based on a series of necropsies on children under 2 years of age which is larger than any we have been able to find in the literature, at least in American literature. The conclusions presented in this paper are based on a series of 374 cases in which a clinical diagnosis of tuberculosis was made in the wards of the Infants' Hospital, and on a series of 138 necropsies in which lesions of tuberculosis were found.

DIAGNOSIS OF TUBERCULOSIS

The material obtained in this study will first be considered in connection with the question of the diagnosis of tuberculosis in the first two years of life. The frequency with which there was found postmortem a tuberculous infection not suspected during life suggested the imperfection of a diagnostic method confined to mere routine examination of the lungs for evidences of consolidation. The incidence of tuberculosis at necropsy is placed by Hamburger at 23 per cent. in babies 1 year old, and at 40 per cent. in babies 2 years old. These figures probably have wide variations according to locality. In our series of 661 consecutive necropsies in children under 2 years, 138, or 20 per cent., showed tuberculous lesions. This frequency suggests how often the presence of the disease is overlooked clinically.

Hamburger divides tuberculosis into three stages, primary, secondary, and tertiary—the primary stage being represented by the primary lesion and the associated lymph node involvement; the secondary stage being represented by all the lesions produced by the further invasion of the body by the tubercle bacillus, and the tertiary stage being represented by the chronic destructive lesions, such as the bone and joint tuberculosis of later childhood, and the phthisis

---

* Received for publication Oct. 10, 1920.

of adult life. We believe that this division into stages is not only advantageous but actually essential in the study of infantile tuberculosis. Every case in the entire series, both clinically and at necropsy, fell clearly and definitely into either the primary or the secondary stage as described by Hamburger.

In looking back over a series of records made before the beginning of the investigation which is the basis of this paper, we were impressed by the fact that the clinical diagnosis of tuberculosis in infancy was based on one of two classes of evidence. The first was the existence of some form of easily recognized clinical tuberculosis, such as tuberculous meningitis, tuberculous peritonitis, or tuberculous pleurisy. The second was the finding in the lung of evidences of chronic consolidation, with such confirmatory evidence as an up and down temperature curve, wasting and, perhaps, a positive von Pirquet reaction. The first class of cases are obviously of the secondary stage of the disease. In the second class of cases, those with evidence of pulmonary consolidation,, the postmortem findings were almost invariably described as tuberculous bronchopneumonia. Therefore, it appears that the diagnosis of tuberculosis, when based on the two classes of evidence mentioned, is really *based on the existence of the secondary stage of the disease,* because tuberculous meningitis, peritonitis, pleurisy and bronchopneumonia are all secondary lesions. This means that in the series of records made before the beginning of the detailed investigation, the diagnosis was only made when the secondary stage had been reached. Meanwhile, necropsies made during the same period every now and then disclosed cases in which no clinical diagnosis of tuberculosis had been made, but in which at the postmortem examination only the lesions of the primary stage were found. It thus appeared that the diagnosis of tuberculosis in infancy in the primary stage was extremely difficult to make under ordinary routine methods of examination.

A study of our necropsy records taken from the period previous to the beginning of this detailed investigation also disclosed another difficulty. It appeared that the existence of chronic signs of pulmonary consolidation, even when associated with an up and down temperature curve and loss of weight, did not warrant a positive diagnosis of tuberculous bronchopneumonia. In many of these cases there was a chronic or unresolved bronchopneumonia, due to another cause, and showing no tuberculous tissue changes. It appeared, therefore, that even when signs of pulmonary consolidation are present, the diagnosis of tuberculosis must depend on more than the ordinary methods of examination. It is only when such definitely recognizable secondary lesions as meningitis or peritonitis are present, that the diagnosis can be made easily.

METHOD OF EXAMINATION

As a result of these observations, the following methods were adopted as a routine in the examination of the babies admitted to the hospital: The lungs were examined not only for signs of consolidation, but also for signs of enlargement of the tracheobronchial lymph nodes. The signs specially looked for were interscapular dulness, prolongation downward of the normal cervical dulness, and d'Espine's sign. The von Pirquet cutaneous reaction was tested, and repeated at intervals. In all cases which showed signs of pulmonary consolidation, or of bronchial lymph node enlargement, or which gave a positive von Pirquet reaction, or in which there was any other reason to suspect tuberculosis, such as exposure or unexplained loss of weight, a roentgenogram of the chest was taken. It proved impossible to carry out this method of investigation as thoroughly as we could wish. With whatever evidence was obtained as a basis, a decision was made as to the presence or absence of tuberculosis. After committing ourselves, the postmortem findings were carefully studied in every case in which a necropsy was performed, and whenever possible the subsequent history of the patients discharged from the hospital with the diagnosis of tuberculosis was followed. We learned a great deal from this procedure, owing to the number of necropsies which were available. It is what we learned that we shall endeavor to present.

TABLE 1.—ANALYSIS OF 374 CASES

	Cases
Diagnosis of tuberculosis made	374
Total admissions to hospital in same period	3,100
Diagnosis confirmed	291
Diagnosis confirmed by necropsy	129
Total necropsies in same period	661
Diagnosis confirmed by subsequent clinical developments	153
Diagnosis remained unconfirmed	78
Diagnosis contradicted by necropsy findings	5
Diagnosis not made clinically in cases found tuberculous at necropsy	9

Table 1 is an analysis of the series with reference to the correctness of the diagnosis made under the methods employed.

The series shows, as a first point of interest, the frequency of clinical tuberculosis in hospital patients under 2 years of age. In 12 per cent. of all our admissions a clinical diagnosis of tuberculosis was made, and in 9 per cent. of all admissions this diagnosis was confirmed. The relative frequency of tuberculosis at necropsy, 20 per cent., is, of course, higher than the clinical frequency, on account of the tendency of the disease to end fatally in the first two years of life.

CONFIRMATION OF DIAGNOSIS

The diagnosis of tuberculosis was considered as confirmed in two ways. One was the finding of tuberculous lesions at necropsy; the

other was the presence or subsequent development of unmistakable clinical types of the disease. The types regarded as unmistakable were typical cases of tuberculous meningitis, peritonitis, pleurisy, or cervical adenitis, or cases showing such clearly tuberculous lesions as Pott's disease or dactylitis, or the clinical finding of tubercle bacilli. No case in which a diagnosis of tuberculous bronchopneumonia or chronic pulmonary tuberculosis was made was placed in this unmistakable group. This confirmation was obtained in some cases by the presence or development of an unmistakable type while the patient was still in the hospital; in other cases it was obtained by the development of such a secondary type in the cases followed through our Social Service Department. Cases in which tubercle bacilli were found in the sputum or in discharging ears were included in this group. There were twenty cases in which tuberculids were found on the skin. The cases in which the diagnosis was confirmed by postmortem examination form the larger group and their number was the most encouraging feature in leading us to continue this method of clinical study.

TABLE 2.—Analysis of the Diagnostic Value of Special Methods of Examination with Reference to Clinical Findings

A. Unmistakable Forms	Cases	Confirmation			Von Pirquet			D'Espine			Roentgen Ray		
		Necropsy	Clinical Development	Unconfirmed	+	0	?	+	0	?	+	0	?
Tuberculous meningitis.............	124	77	47	0	46	26	1	40	21	13	38	2	8
Tuberculous peritonitis...............	19	4	11	4	9	7	2	1	13	1	1	5	3
Tuberculous pleurisy	1	0	1	0	1	0	0	1	0	0	1	0	0
Tuberculous cervical adenitis............	1	0	1	0	1	0	0	0	0	1	1	0	0
Bone and joint tuberculosis..........	1	0	1	0	1	0	0	1	0	0	0	0	1
Total............	146	81	61	4	58	33	3	43	34	15	41	7	12
B. Forms Presenting Difficulty in Diagnosis:													
Chronic primary tuberculosis.........	135												
a. Pulmonary.......	126	2	58	66	76	37	7	71	12	53	68	8	18
b. Intestinal........	9	2	2	5	3	2	0	0	9	0	1	8	0
Tuberculous bronchopneumonia......	34	10	21	3	16	15	1	20	9	14	20	0	8
Miliary tuberculosis (without meningitis)	54	43	11	0	25	23	0	24	17	11	28	1	5
Total............	223	57	92	74	120	77	8	115	47	78	117	17	31
Grand total.....	369	138	153	78	178	110	11	158	81	93	158	24	43

Table 2 shows the series of cases analyzed with reference to the clinical diagnosis, and the presence or absence of the evidence through which the forms presenting difficulty in diagnosis are to be recognized.

It will be noted that in many cases the von Pirquet test, the examination of the chest for interscapular dulness and d'Espine's sign or

the roentgenogram were negative. Nevertheless, in the second group, showing the presence or absence of these signs in forms of tuberculosis presenting difficulty of diagnosis, *a diagnosis of tuberculosis was not made in any case unless at least one of these three signs was positive.*

Table 3 shows the presence or absence of the same three signs, taken not with reference to the clinical diagnosis, but with reference to the confirmation of the diagnosis by necropsy or otherwise. Of course, in all the cases of tuberculous meningitis in the series the diagnosis was also confirmed by lumbar puncture.

TABLE 3.—The Diagnostic Value of Special Methods of Examination with Reference to Necropsy Findings

	Cases	Von Pirquet			D'Espine			Roentgen Ray		
		+	0	?	+	0	?	+	0	?
A. Confirmation by necropsy................	143	59	37	2	80	32	31	48	11	18
1. Primary lesions only....	4	3	1	0	2	2	0			
a. Lung................	2	1	1	0	2	0	0	1	0	1
b. Intestine.............	2	2	0	0	0	2	0	0	2	0
2. Secondary lesions found.................	125	53	30	0	74	22	29	44	9	15
3. Clinical diagnosis not made; necropsy showed primary lesions of tuberculosis...........	9	0	5	0	0	7	2	None made		
3. Clinical diagnosis of tuberculosis; necropsy failed to confirm......	5	3	1	0	4	1	0	3	0	2
B. Confirmation by clinical developments.........	153	61	51	5	44	32	27	85	8	17
C. Clinical diagnosis unconfirmed.............	78	61	23	6	38	18	35	28	5	10
Total..................	374	181	111	11	162	82	93	161	24	45

DIAGNOSTIC VALUE OF TUBERCULIN TEST

The von Pirquet reaction was present in the majority of cases. Comparison of our results with necropsy findings would suggest that the reactions designated as "suspicious" or "doubtful," should in the infant be considered as positive for purposes of diagnosis. Nevertheless, the reaction was negative in a fairly large proportion of cases in which the diagnosis of tuberculosis was confirmed either by necropsy, or by the development of some unmistakable type of secondary lesion. We believe that the comparatively high proportion of negative von Pirquet reactions obtained in tuberculous infants under 2 years is to be explained by the frequency of marked atrophy and anemia, which prevents the showing of a positive test. We must assume from our results that the presence of a negative von Pirquet in no way rules out the diagnosis of tuberculosis in an infant under 2 years of age.

The diagnostic value of a positive von Pirquet reaction in the infant appears to be much greater. In only five cases in our series

did the necropsy findings fail to confirm the clinical diagnosis of tuberculosis. In only three of these cases was the von Pirquet reaction recorded as positive. It is, therefore, safe to conclude that in an infant under 2 years of age, a diagnosis of tuberculosis with very little chance of error may be made when a positive von Pirquet reaction is obtained.

DIAGNOSTIC VALUE OF PHYSICAL SIGNS

The examination of the chest for interscapular dulness and d'Espine's sign is important. When no spinal dulness or bronchial breathing is obtained below the level of the second dorsal vertebra, the sign should be considered negative. When the level is the third dorsal vertebra, the sign should be considered as doubtful, and no conclusion can be based on these signs alone. When the spinal dulness and bronchial breathing are found below the level of the third dorsal vertebra, the sign should be considered as positive in cases without signs of pulmonary consolidation, and a diagnosis of tracheobronchial lymph node enlargement, presumably tuberculous, may be made. When there are signs of consolidation of the lung, they often mask d'Espine's sign and interscapular dulness, and caution must be exercised. Tuberculosis should not be diagnosed without other evidence in these cases. In our series, this method of examination was positive in 48 per cent., doubtful in 27 per cent. and negative in 25 per cent. It was negative in 22 per cent. of the cases which came to necropsy. In the primary stage of the disease, our necropsy statistics suggest that a diagnosis of tuberculosis based on a positive d'Espine's sign or interscapular dulness, or both, will be right in the majority of cases. A negative finding does not rule out tuberculosis, and is of course always the rule in cases of primary intestinal tuberculosis.

DIAGNOSTIC VALUE OF ROENTGENOGRAMS

The examination of roentgenograms of the chest eventually proved to be the diagnostic method on which we placed the greatest reliance. Practice in interpreting plates is necessary, and this can only be gained by the comparison of clinical conclusions with necropsy findings. It is necessary to know what tuberculous lesions of the chest are shown and what are not shown in roentgenograms. Four lesions in the chest are characteristic of the tuberculosis of infancy. These are, first, primary lesions in the lung; second, the accompanying enlargement and caseation of the tracheobronchial lymph nodes; third, miliary tuberculosis of the lung, and fourth, tuberculous bronchopneumonia.

The primary lesion of the lung is usually not shown in the rentgenograms; it is too small. There were only one or two cases in our series in which there was found at necropsy a primary lesion large

enough to give a shadow on a photographic plate. The enlargement and caseation of the bronchial lymph nodes can be seen in the majority of roentgenograms. This appears as a definite and characteristic shadow at the hilus of the lung, but much practice is required in distinguishing this shadow from certain shadows found at the hilus in normal infants. Congenital pulmonary atelectasis and thymic enlargement occasionally lead to a mistaken diagnosis. Acute miliary tuberculosis of the lung does not show in roentgenograms in the majority of instances. This is proved by a large series of negative roentgenograms obtained in cases showing this lesion at the necropsy. In the earlier cases of our series we frequently made a diagnosis of acute miliary tuberculosis of the lungs when the plates showed a peculiar spotted appearance. In the majority of cases of this kind which came to necropsy, the postmortem finding was tuberculous bronchopneumonia. Nevertheless, there were in the series a few spotted plates which showed no bronchopneumonia but showed a miliary tuberculosis of the lung with the formation of large conglomerate tubercles. Finally, tuberculous bronchopneumonia invariably shows in roentgenograms a shadow recognizable as pulmonary consolidation, but not always recognizable as tuberculous. We shall have more to say about these plates in considering the diagnosis of this form of infantile tuberculosis.

Roentgenograms of the chest were positive in 70 per cent. of the observations made in our series; positive or suspicious in 89 per cent.; negative in 11 per cent. These figures show their great diagnostic value in tuberculosis of the first two years of life. Necropsy findings also suggested that most of the roentgenograms recorded as doubtful or suspicious should have been considered positive. Negative roentgenograms in cases which came to necropsy were recorded in only 14 per cent. We may, therefore, conclude that a diagnosis of tuberculosis may be made by any one practiced in interpreting roentgenograms whenever the roentgenogram is positive for tracheobronchial lymph node enlargement. A negative plate, however, does not rule out tuberculosis.

DIAGNOSIS OF THE PRIMARY STAGE

In general, as far as the diagnosis of the primary stage of tuberculosis is concerned, the following conclusions appear to be warranted: A positive von Pirquet reaction is the only evidence pointing toward a primary intestinal infection, and the diagnosis of this form of the disease cannot be made unless either the von Pirquet is positive or the physician is fortunate enough to find tubercle bacilli in the stools. Primary intestinal tuberculosis is, however, very rare in comparison with a primary focus in the lung, and it is in the recognition of this

latter condition that special methods of diagnosis are particularly needed. If either the von Pirquet reaction is positive or even suspicious, or if the roentgenogram of the chest shows the shadow characteristic of tracheobronchial lymph node enlargement, a diagnosis of tuberculosis primary in the lung may be made with a fair degree of certainty. If the sole evidence is a positive or even suspicious d'Espine's sign, or interscapular dulness, the diagnosis may be made with only a slight degree of probability.

TABLE 4.—Diagnostic Signs in Cases Showing Physical Signs of Pulmonary Consolidation

Necropsy Findings	Cases	Von Pirquet			D'Espine			Roentgen Ray		
		+	0	?	+	0	?	+	0	?
Tuberculous broncho-pneumonia	42	21	10	1	38	1	3	20	1	5
Chronic primary tuberculosis plus nontuberculous pneumonia	4	3	0	0	2	1	1	1	0	3
Nontuberculous pneumonia without primary tuberculous lesions	5	3	1	0	4	1	0	3	0	2

In all cases in which all three of these forms of evidence are absent, tuberculosis in the primary stage should not be diagnosed. In cases of the secondary stage of the disease the diagnosis so frequently depends on ordinary clinical evidence that these special methods of investigation are unnecessary. There are, however, two secondary forms of the disease in which the diagnosis is more difficult. These are tuberculous bronchopneumonia and general miliary tuberculosis involving the lung and abdominal organs but in which the brain is spared.

POSITIVE DIAGNOSTIC VALUE OF PULMONARY CONSOLIDATION

The characteristic sign of tuberculous bronchopneumonia in the infant is the finding of evidence of pulmonary consolidation. In general, these cases tend toward a rather chronic course, but some of them are fully as acute as ordinary cases of nontuberculous pneumonia. No very reliable conclusion can be drawn from the extent and distribution of the consolidation as shown by physical examination. It is important in all these cases to determine whether the consolidation is due to a tuberculous pneumonia or to a pneumonia from some other cause. For this purpose we must rely on the same general signs of tuberculosis as we have considered in connection with the primary stage of the disease, namely, the von Pirquet reaction, the examination of the chest for signs of tracheobronchial lymph node enlargement, and the results of roentgenograms of the chest.

Table 4 shows these diagnostic signs in the cases of our series in which a diagnosis of tuberculous bronchopneumonia was made and confirmed at necropsy findings.

We may conclude from these statistics that in the majority of cases showing pulmonary consolidation, in which either the von Pirquet reaction or the roentgen ray is positive, the correct diagnosis is tuberculous bronchopneumonia. In a few cases, however, the diagnosis of tuberculosis will either be wrong, or else there will be a combination of the primary stage of tuberculosis with a nontuberculous pneumonia. Roentgenograms will usually permit the observer to distinguish between tuberculous and nontuberculous pneumonia. · In the tuberculous form the shadows are much more distinct and sharply outlined. Many plates show the characteristic speckled or spotted appearance which is never seen in nontuberculous pneumonia. When there are large areas of consolidation the shadows are usually much more dense than in nontuberculous pneumonia. It should be remembered, however, that occasionally a speckled or spotted plate means acute miliary tuberculosis of the lung with conglomerate tubercle formation and without the lesion of pneumonia. Such cases may, however, be recognized through the absence of signs of consolidation of the lung on auscultation and percussion.

PROGNOSIS

The analysis of the outcome of the disease to date in the cases in our series as shown by the hospital mortality and the subsequent mortality or present condition of the cases discharged from the hospital, is interesting as bearing on the prognosis of tuberculous infection when acquired during the first two years of life. This is shown in Table 5.

TABLE 5.—Outcome in 369 Cases Diagnosed as Tuberculosis

	Cases
Died in hospital	194
Discharged living	175
Present condition unknown	50
Present condition known	125
Died after discharge	82
Alive and well	43

The mortality in the hospital was as high as 53 per cent. This, of course, does not give any accurate idea of the fatality of tuberculous infection in the first two years of life, because infants who seek hospital treatment are apt to show the more serious forms of the disease. It does suggest, however, the great prevalence of acute and fatal forms of the disease in the first two years of life.

Of the patients who died in the hospital, the cause of death in 188 was the existence or development of some severe form of the

secondary stage of the disease. Of these secondary forms, tuberculous meningitis was the most common, tuberculous bronchopneumonia standing next in frequency. (Miliary tuberculosis without meningitis was a rare clinical diagnosis, but was the most common lesion found at necropsy, being present in almost every case of tuberculous meningitis, in many cases of tuberculous pneumonia, and occasionally being the only secondary lesion.) In the remaining six cases, only the lesions of the primary stage were found, and to these may be added the nine cases in which the diagnosis was not made during life, which also showed only lesions of the primary stage. In these fifteen cases, the tuberculosis could only be considered a contributing cause of death, as all the patients were admitted to the hospital for functional cases of that character.

TABLE 6.—DIAGNOSIS AT DISCHARGE AND FINAL OUTCOME IN 175 CASES

	Cases	Living	Died	Lost
Primary stage..	123	38	43	42
Tuberculous meningitis...............................	14	0	14	0
Tuberculous bronchopneumonia.....................	14	1	11	2
Tuberculous peritonitis..............................	14	0	8	6
General miliary tuberculosis........................	7	1	6	0
Tuberculous cervical adenitis.......................	1	1	0	0
Tuberculous pleurisy.................................	1	1	0	0
Bone and joint tuberculosis........................	1	1	0	0
Total...	175	43	82	50

Of the patients discharged from the hospital, the diagnosis at the time of discharge with the present condition of the patient is shown by Table 6.

This table shows that the majority of the patients now living showed at the time of their discharge from the hospital only the primary stage of the disease. The patients in this stage who were followed to a subsequent fatal ending all developed a serious secondary form which was the cause of death. It is also an interesting fact that *this secondary form usually developed within a comparatively short time after discharge, usually within the period of infancy, that is, before the end of the second year of life.*

We may conclude from the subsequent history of these cases, that *the prognosis of infantile tuberculosis is best when the patient shows evidence that the disease has not advanced beyond the primary stage, but is still not good,* owing to the tendency of the infant to develop fatal forms of the secondary stage. This tendency is greatest in infancy, grows less as the child grows older.

The figures from the forms of the secondary stage show that only tuberculous meningitis or general miliary tuberculosis are absolutely fatal. In all the other forms of tuberculosis there is a possibility of

recovery, but the prognosis is much worse than in the primary stage. In the first place, these types may be fatal in themselves, tuberculous bronchopneumonia being the most serious next to the miliary forms. Not only, however, is there this danger, but also in all these forms there is the same tendency toward the development of meningitis or miliary tuberculosis as was seen in the primary stages, this tendency being greatest in infancy.

If it were not for this tendency, characteristic of infancy, toward the development of severe secondary forms of tuberculosis, we would have little evidence of the value of our diagnostic methods in recognizing the disease while the patient was still in the primary stage. Comparatively few persons whose condition was diagnosed as being in this stage of the diease came to necropsy; the majority left the hospital alive. But their subsequent histories and mortality substantiated the diagnosis so frequently, that we believe that the recognition of the primary stage of the disease can be made in most cases through the use of the von Pirquet reaction, roentgenograms, and careful examination for the physical signs of tracheobronchial lymph node enlargement. The importance of making the diagnosis in this stage is evident from the peculiarities of the prognosis of tuberculous infection acquired in infancy. This prognosis is bad. Would it be so bad if the presence of tuberculosis in the infant were recognized earlier, and proper treatment instituted as early as possible? This could only be done by means of a systematic and thorough examination of every infant with special reference to tuberculosis. We believe that the physician should consider the possibility of tuberculous infection in the case of every infant that comes under his care. That the infant shows no evidence of being sick should make no difference, for if the disease is in the primary stage, no symptoms suggesting tuberculosis are manifested, but the child will either seem well, or else present itself as a "feeding case," showing only symptoms of functional gastro-intestinal disturbance.

We have heard the very harmful and meaningless word "pretuber-culous" applied to infants. We have heard the term "latent" or "inactive" tuberculosis applied to infants with the implication that there was little or no danger. Physicians should recognize that an infant is either tuberculous or it is not. If there is one tubercle bacillus, or the smallest tuberculous lesion within the body, the infant is tuberculous. There is no "healed tuberculosis" in the infant. If the tuberculous lesion is latent, inactive, it is better than if the infant had tuberculous meningitis, but the infant is none the less in danger. It is not difficult to make the von Pirquet test on every infant seen, nor to examine the back for interscapular dulness and d'Espine's sign.

Often the diagnosis can be made without a roentgenogram, but one should be made in as many cases as possible.

We believe that if this procedure were more generally carried out, many more cases of infantile tuberculosis would be recognized while in the primary stage. There is so little provision near Boston for the proper treatment of tuberculous infants, that we cannot quote results, but we believe that with earlier recognition of tuberculosis in the infant and with the institution of appropriate treatment, there would be fewer cases seen of dangerous or fatal secondary stage forms, fewer deaths, fewer despairing mothers receiving the verdict which goes with tuberculous meningitis, and asking how such a thing could have occurred in a baby who has always seemed so well.

A NEW APPARATUS AND METHOD FOR PUNCTUR-
ING THE SUPERIOR LONGITUDINAL
SINUS IN INFANTS *

A. BRET RATNER, M.D.

NEW YORK

The use of the superior longitudinal sinus to obtain blood for examination and as a path for intravenous injections is attended with many advantages. These advantages are readily appreciated and are emphasized in a number of recent papers. The first to use this vessel was Marfan,[1] in 1898, for the introduction of salt solution in a case of cholera infantum. Nothing further appeared in the literature regarding its use until 1915, when Tobler [2] studied the anatomic relations of the sinus for this purpose. While sinus therapy is now generally regarded a safe procedure, the fact, however, that the sinus is hidden from view, and that there is danger of infiltration into the brain when injecting fluid, justifies a consideration of technic.

Goldbloom,[3] in 1918, devised an apparatus which was an improve ment upon several which preceded it. In March, 1920, he [4] described a new apparatus in which the block was beveled at an angle of 5C degrees. The great disadvantage of Goldbloom's apparatus is that the block is so large (and the beveled block gives even a larger surface) that it entirely obliterates the point of the needle from view. It is obvious, therefore, that to insert the needle into the exact spot decided on is somewhat a matter of chance. The fact that in the improved apparatus the needle enters at an angle of 50 degrees does not eliminate the possibility of injury to the sinus wall, as the angle is not sufficiently acute to make the needle run parallel with the sinus after it has been entered. If the needle has been set too long and put in obliquely, it may transfix or penetrate the wall of the sinus. Other disadvantages are that the apparatus is very expensive and a special needle is required should it become too dull for use.

1. Marfan (from Blechmann, G.): Technique des prélévéments de sang et des injections intraveineuses chez les nourrissons, Le Nourrisson 2:150, 1914.

2. Tobler, L.: Zur technic der diagnostischen blutentnahme und der intravenösen injection beim saügling, Monatschr. f. Kinderh. 13:384, 1915.

3. Goldbloom, A.: A New Apparatus for Puncture of the Superior Longitudinal Sinus, Am. J. Dis. Child. 16:388 (Nov.) 1918.

4. Goldbloom, A.: An Improved Needle for Sinus Therapy, Am. J. Dis. Child. 19:229 (March) 1920.

Owing to disadvantages of the various methods in use, I have devised an apparatus which is simple, inexpensive and presents, I believe, many advantages. It has been used on a large number of infants in the New York Nursery and Child's Hospital and has proved satisfactory.
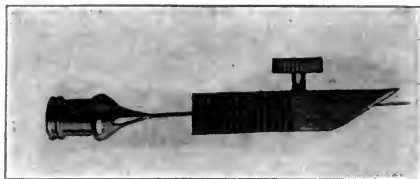
Fig. 1.—Author's Apparatus.

It consists of a small metal block, $\frac{1}{4}$ of an inch square by $1\frac{1}{4}$ inches long, with an acutely beveled base. An opening of 18 gage bore runs through the middle of the block which permits the insertion of the needle. A thumb screw is provided which holds the needle securely in place after it has been adjusted to the desired length. The needle is $1\frac{3}{8}$ inches long with a Luer-slip hub and a short beveled point.
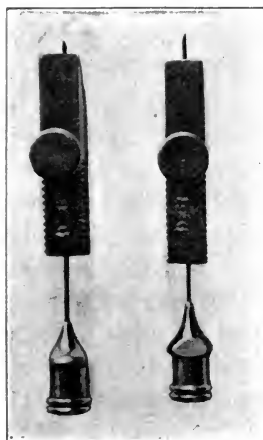
Figure 2

Figure 3

Fig. 2.—Position to adjust length of needle.
Fig. 3.—First step for injecting fluid.

The first step in using the apparatus is to determine the length of the needle necessary to just enter the sinus. There is no exact way of doing this as the depth of the sinus varies somewhat in different infants. A method which I have found helpful is to pinch up a portion of the scalp and half the thickness of the fold gives the approximate depth into the sinus. With the needle as in Figure 2, it is adjusted to the length decided on and the set screw is tightened, keeping

the bevel of the needle in the same direction as the bevel of the block. Tobler's measurements show that the distance from the skin to the sinus is from 2 to 5 mm. and the depth—at the posterior angle—varies between 4 and 7 mm., depending on the age and size of the infant. This would give a range of from 3 to 6 mm. to just enter the sinus in the various cases. Keeping these figures in mind serves as a control.
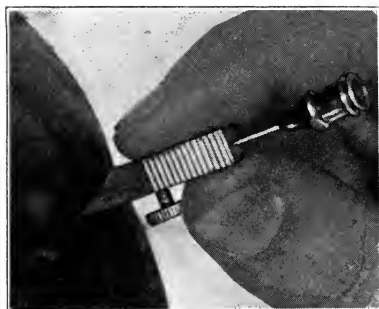
Fig. 4.—Second step for injecting fluid.

Figure 5

Figure 6

Fig. 5.—Third step for injecting fluid.
Fig. 6.—First step for collecting blood.

The point of entrance is chosen near the posterior angle of the fontanel along an imaginary line drawn between the middle of the bridge of the nose and the posterior angle of the fontanel. For the administration of fluid the apparatus, held as in Figure 3, is forced in—at the point decided on—up to the end of the block (Fig. 4). If one has successfully entered the sinus, there will be an immediate and steady flow of blood, and now using the end of the block as a fulcrum, the apparatus is quickly turned so as to bring the beveled

surface of the block in close apposition to the scalp (Fig. 5). A syringe or gravity apparatus is immediately attached to the hub, and the fluid is administered in the usual manner. When the operation is completed, the needle is pulled out, a compress is held firmly over the bleeding point, and the child is raised to a sitting position. After the bleeding has stopped, collodion is applied. For the collection of blood the apparatus is used as shown in Figures 6, 7 and 8.

If one has not entered the sinus successfully, the needle may have been set too short or too long. It may have become blocked, or it may have been inserted outside the sinus. Under such conditions it is time saving immediately to withdraw the needle, determine where the fault lies and correct it. Whenever the needle has been used, it should immediately be cleansed with running cold water;

Figure 7

Figure 8

Fig. 7.—Second step for collecting blood.
Fig. 8.—Third step for collecting blood.

the wire run through with a cleaning powder or sapolio until the lumen is clean, rinsed in cold water, then alcohol, and finally immersed in ether. This will keep the apparatus in perfect condition and obviate another cause of faulty venipuncture.

The advantages of this apparatus are that it is of simple construction; the needle is always in view when inserting it; it can be held comfortably and firmly in place. The end of the block prevents the needle from entering too far and serves as a fulcrum upon which the block turns, automatically causing the needle to assume a plane in the direction of the sinus. The beveled surface lying flat against the scalp prevents lateral movement and keeps the needle in a constant position. Any ordinary needle with a short bevel up to an 18 gage can be used.

CLINICAL DEPARTMENT

CASE OF MENINGITIS DUE TO THE BACILLUS ACIDI-LACTICI

OCCURRING IN A PREMATURE INFANT ONE MONTH OLD *

ROY M. GREENTHAL, M.D.

ANN ARBOR, MICH.

The occurrence of meningitis in the new-born and infants under three months of age is said to be uncommon. Barron,[1] in 1918, was able to collect only thirty-nine cases. Of these fourteen were due to the colon bacillus. It was thought that the report of an additional case would prove of interest, especially as the causative agent was the *Bacillus acidi-lactici*. In a search of the literature I can find no mention of this organism causing a meningitis.

REPORT OF CASE

L. P., a negro girl, aged 1 month, was admitted to the pediatric service of the New York Nursery and Child's Hospital, April 16, 1920. Chief complaint convulsions followed by stupor.

Family History.—Mother died of tuberculosis two weeks after the birth of the patient.

Birth History.—Child was born prematurely at seven months. Birth weight, 4 pounds.

Feeding History.—Has been receiving a skimmed milk mixture. Details unknown.

Past Illness.—None.

Present Illness.—Seven days prior to entrance the baby began to refuse its feedings and appeared ill. No fever noticed at this time. Five days later the patient had two generalized convulsions, each lasting about five minutes. There had been no vomiting at any time. No stiffness of the neck nor any retraction were noticed. The baby had gradually become more apathetic, and for the last twenty-four hours was stuporous.

Physical Examination.—Patient is a very poorly nourished negro infant nearly moribund. Lies in a stupor with eyes half closed. Respirations very shallow and irregular. Cannot be aroused to notice objects. Anterior fontanel is very tense and bulging. Pupils contracted; equal; react very sluggishly to light. No discharge from external auditory canals. Tympanic membranes cannot be seen. Tongue and mucous membranes very dry and covered with thrush. No rigidity of neck, nor any retraction. Heart sounds are very rapid, no murmurs heard. Few coarse râles heard over bases of both lungs. Abdomen

1. Barron: Am. J. M. Sc. **156**:365, 1918.

is sunken; spleen not felt. No Kernig or Brudzinski. Tache cérébrale not present. The skin shows evidence of moderate dehydration. Temperature, 98.4 F. Weight, 4 pounds 13 ounces.

Laboratory Findings.—Leukocytes, 19,400. Polymorphonuclears, 58 per cent.; lymphocytes, 42 per cent. Urine specimen not obtained. Von Pirquet negative at twenty-one hours. Lumbar puncture: 10 c.c. of thick purulent fluid under moderate pressure. The fluid was pure white in color and on standing a short time gave the appearance of curdled milk. Globulin test, $+ + + +$. Sugar, negative. Stained smears showed the cells to be nearly all polymorphonuclear. Numerous gram-negative bacilli were seen, both intracellular and extracellular. The bacilli varied in size from long rods to coccoid forms.

Six hours later a ventricular puncture was performed and 35 c.c. of thin purulent fluid was withdrawn. Twenty c.c. of antimeningococcus serum was injected into the ventricles. Ventricular fluid: Cell count, 3,000 per c.mm.; 98 per cent polymorphonuclears. Globulin, $+ +$. Sugar, negative. Stained smears showed the same gram-negative bacillus. The general condition of the patient grew steadily worse. Temperature rose to 106 F. Brownish bile-stained fluid was vomited. Continuous coarse twitching movements were noticed. Death occurred twenty-one hours after admission.

Necropsy.—(Seventeen hours after death) April 17, 1920. The body is that of a poorly nourished negro girl. Length, 19 inches. Weight, 4 pounds 14 ounces. The principal pathology is intracranial. The entire surface of the brain is covered with a thick greenish yellow exudate. This is more marked over the right side. The convolutions are entirely flattened out. Cut sections show marked congestion and edema. The ventricles are slightly dilated and filled with a thin purulent fluid. The right antrum and middle ear are filled with pus. Smears from the cortex and right middle ear show the same gram negative bacillus found in the spinal and ventricular fluids. The microscopic sections of the brain show a purulent lepto-meningitis with marked congestion and edema of the cortex. The rest of the examination was practically negative. There was no pneumonia, nor was any evidence of tuberculosis found. The bladder urine was negative for albumin and leukocytes.

Anatomic Diagnosis: Acute purulent leptomeningitis; acute purulent otitis media (right).

The Organism: Cultures from the spinal fluid obtained from the first lumbar puncture were made on plain nutrient agar and bouillon. The agar tubes showed a profuse moist spreading grayish growth in eighteen hours. The bouillon cultures became cloudy in nine hours. After eighteen hours the tubes were very cloudy with a marked sediment at the bottom. Smears from the agar and bouillon cultures showed a pure culture of a gram-negative coccoid bacillus. Hanging drop showed a motile bacillus.

Fermentation Reactions (courtesy of Dr. Harold Amoss of the Rockefeller Institute): Glucose, mannite, levulose and lactose were fermented with the production of gas and acid. Saccharose, inulin, dextrin and salicin were unattacked.

According to the classification of Kliger[2] and Levene,[3] the organism is the *Bacillus acidi-lactici,* one of the colon group.

<div align="center">COMMENT</div>

The diagnosis of meningitis in very young infants is very difficult, the condition often being unsuspected during life. The only physical signs in this case were the stupor and bulging fontanel. The history of tuberculosis in the mother was suggestive of tuberculous meningitis

2. Kliger: J. Infect. Dis. **15**:187, 1914.
3. Levene: J. Bacteriol. **3**:253, 1918.

in the patient. After the lumbar puncture it was thought that we were dealing with a colon bacillus infection until the fermentation reactions were performed. However, the gross appearance of the spinal fluid was quite different from that usually described in colon meningitis (a dark brownish purulent fluid with an offensive odor). The fluid in this case was pure white in color, it had no odor, and on standing looked like curdled milk.

The portal of entry in this case was probably through the right middle ear. No other focus was found at necropsy. The causation of meningitis by an organism such as the *B. acidi lactici* can probably be explained by the fact that the patient, a premature infant, very poorly nourished, had not sufficient resistance to overcome even this ordinarily harmless saprophyte.

HEART DISPLACEMENT APPARENTLY DUE TO MEDIASTINAL EMPHYSEMA FOLLOWING ASPIRATION PNEUMONIA *

E. C. FLEISCHNER

SAN FRANCISCO

Heart displacement in children is ordinarily due to the presence either of free fluid or free air in the pleural cavity. The following case illustrates a marked type of displacement of the heart to the right in which neither pleuritic effusion, hydrothorax nor pneumothorax played a rôle.

REPORT OF CASE

G. P., aged 4 years, Sept. 10, 1919, at 4 p. m., fell into a pile of sand, and on being picked up by his mother stated that he had swallowed some of the sand. No effect was evident at that time, but when the boy was put to bed at 6 p. m., two hours after the accident, musical sounds were heard all over his chest, and he was breathing very rapidly.

He was taken to the Children's Hospital four hours after the accident, at which time physical examination revealed nothing beyond the presence of a large number of sibilant and sonorous râles over both lungs anteriorly and posteriorly. Roentgen-ray examination made one day after the accident was negative (Figure 1). Temperature and pulse were practically normal for about forty-eight hours. Five days after the aspiration of the sand, there were definite signs of bronchopneumonia on the left side, particularly over the middle lobe. Eight days after the accident, physical examination disclosed that the heart was very markedly displaced to the right. Roentgen-ray examination at that time showed a profuse bronchopneumonia of the left lung and the heart very markedly pushed to the right side (Figure 2). The explanation of this displacement was not apparent for six days. September 24, subcutaneous emphysema developed suddenly in the supraclavicular space on the right side, extending upward, backward and downward over the right lung posteriorly as far as the pelvis. On account of the very serious general condition of the child, roentgenogram was not taken at that time. The air under the skin was gradually absorbed. At the end of one week it was no longer apparent.

October 7, about two months after the accident, roentgen-ray examination revealed (Figure 3) the heart still markedly displaced to the right with a diffuse pneumonic process of the left lung, which at this time involved the lower lobe more than on previous examination. The patient continued to have a septic temperature; he coughed a great deal, and on physical examination, besides the heart displacement, showed diminished breathing all over the left lung, bronchovesicular in character, with a variety of adventitious sounds. He was returned to his home. His temperature became very much more septic in character; he emaciated more rapidly and expectorated large quantities of purulent sputum. Bronchiectasis was suspected. He was taken back to the hospital, a fourth roentgenogram (Figure 4) was taken which showed a diffuse bronchopneumonia still present with small bronchiectatic cavities.

POSTERIOR

RIGHT

LEFT

SEPT 18 1919

1 WEEK AFTER ACCIDENT

BRONCHO PNEUMONIA OF LEFT LUNG WITH HEART
DISPLACEMENT BEFORE APPEARANCE OF SUBCUTANEOUS
EMPHYSEMA

Figure 2

LEFT

RIGHT

SEPT 11 1919

1 DAY AFTER ACCIDENT
SIGNS OF ASTHMATIC BRONCHITIS

Figure 1

RIGHT   LEFT

BRONCHO-PNEUMONIA MORE ADVANCED IN LOWER LOBE
WITH HEART DISPLACEMENT AFTER DISAPPEARANCE
OF SUBCUTANEOUS EMPHYSEMA   OCT 7 1919

Figure 3

RIGHT   LEFT

BRONCHIECTASIS OF LEFT LUNG   NOV 25 1919
HEART STILL DISPLACED TO RIGHT BUT LESS MARKED

Figure 4

RIGHT CLAVICLE
LEFT CLAVICLE
L U N G
9 CM
5 CM
SPONTANEOUS PNEUMO THORAX
CATALDO
JUNE 14,1915
34 136

Figure 6

LEFT
RIGHT
MAR 19 1920
APPARENTLY NORMAL 6 MONTHS AFTER ACCIDENT
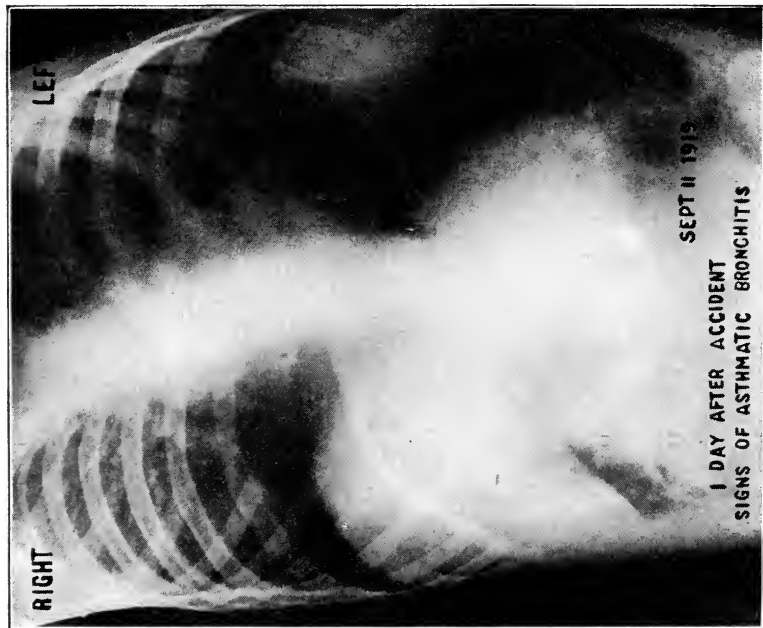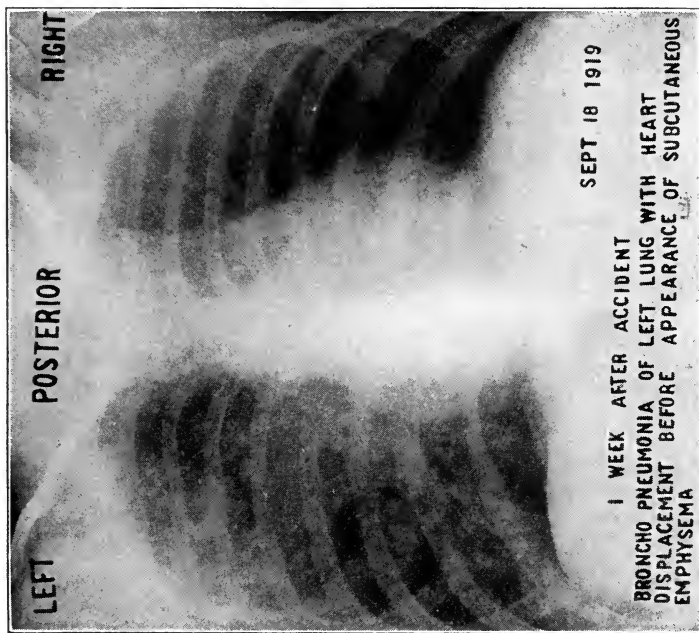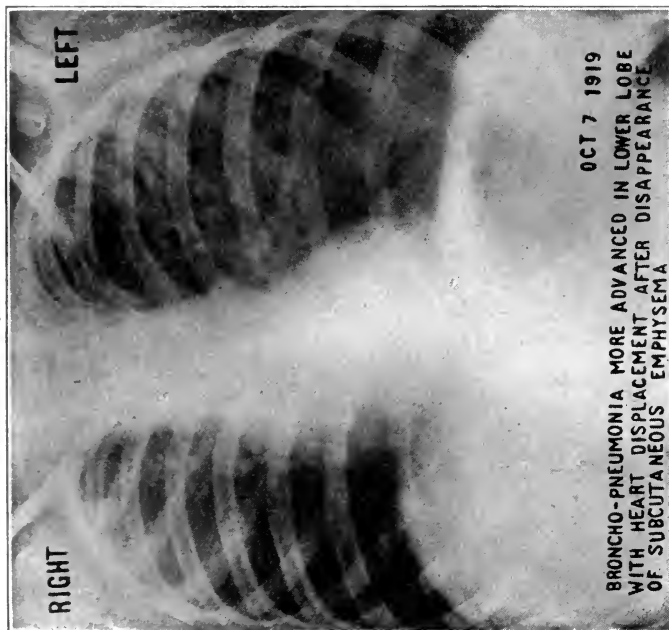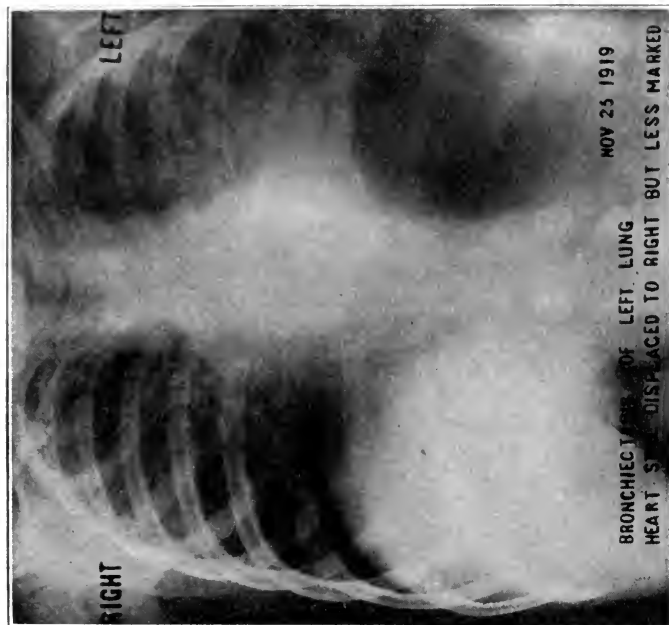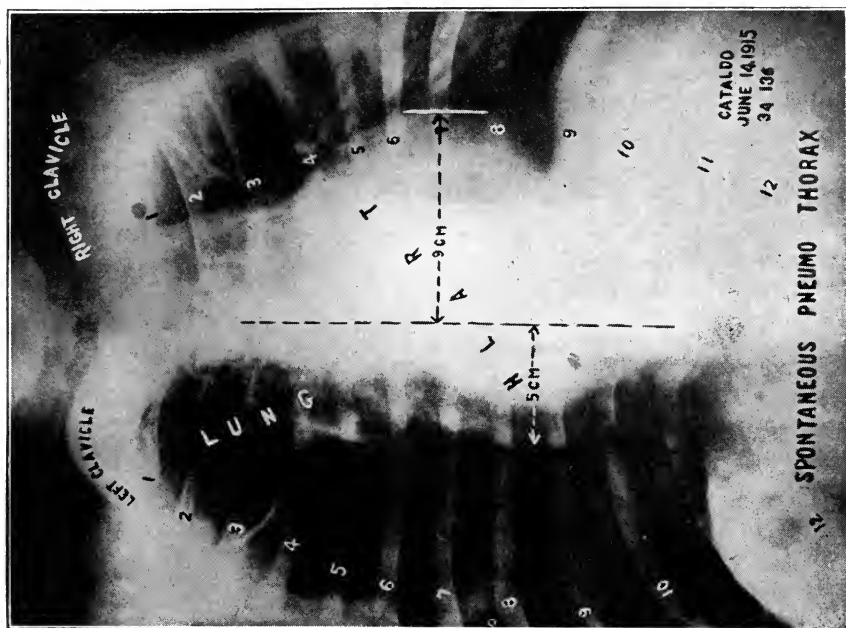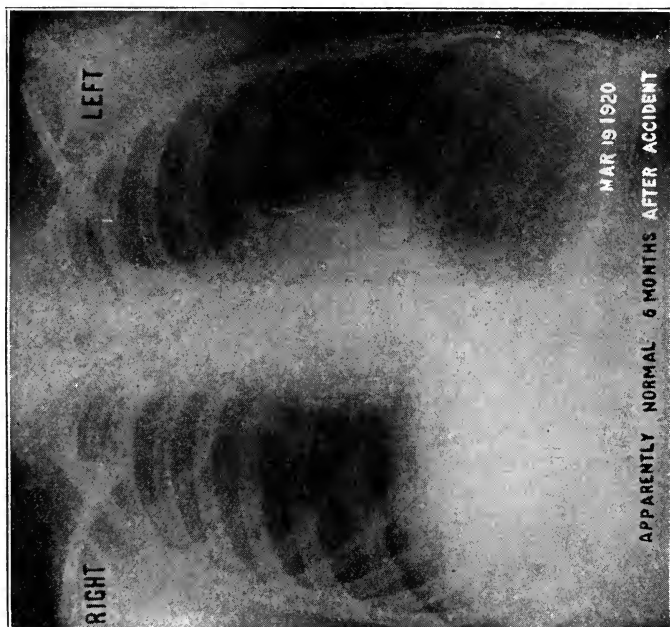
Figure 5

The child was then taken to the country and was not seen for several months. His temperature gardually reached normal, his cough diminished, the amount of sputum grew progressively less; he gained weight and was brought back March 19, 1920, about six months after the original accident. Physical examination was negative and the last roentgenogram (Figure 5) taken at that time showed an apparently normal chest.
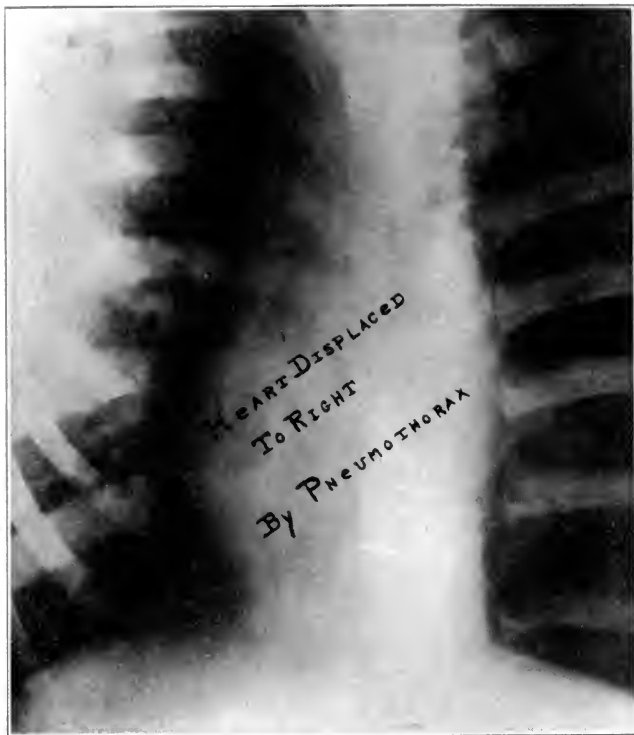
Figure 7

COMMENT

The case is essentially interesting on account of the marked displacement of the heart which was apparently due to the rupture of some of the air vesicles of the inflamed lung allowing free air to escape into the mediastinum, from which it made its way up under the right clavicle and posteriorly over the right side. Were it not for the fact that subcutaneous emphysema manifested itself, it would have been very difficult to have excluded an intense interstitial emphysema of the left lung as the cause of the displacement, but considering the fact that the air escaped from the inflamed lung and not having been able to prove its presence in the pleural cavity, one is forced to the conclusion that the heart could only have been displaced by the presence of air in fairly large quantities in the mediastinum.

A careful review of the literature fails to disclose any record of a similar observation.

THE NATURE OF THE REDUCING SUBSTANCE IN THE URINE OF INFANTS WITH NUTRITIONAL DISORDERS [*]

OSCAR M. SCHLOSS, M.D.

NEW YORK

The occurrence of a reducing substance in the urine of infants affected with gastro-enteric or nutritional disorders has long been recognized. Grosz [1] examined the urine of fifty breast fed infants and the urine of ten reduced Trommer's and Nylander's solutions. In no case did the urine ferment with yeast. Most of the positive results were from infants ill with gastro-enteric disorders. Grosz observed that melituria diminished when tea was substituted for breast milk, and again increased when the diet of breast milk was resumed. He thought that the reducing action of the urine was due to lactose or to a split product of lactose.

Orban [2] concluded that the reducing substance which commonly occurs in the urine of infants with gastro-enteric disturbances is lactose. Tests of the feces in such cases showed the absence of lactase, the ferment which splits lactose into glucose and galatose. It is well known that unaltered lactose cannot be utilized by the organism. If lactose enters the blood stream, it is eliminated in the urine. Due to the supposed absence of the specific lactose splitting enzyme (lactase), Orban considered that unchanged lactose was absorbed with resulting lactosuria.

Langstein and Steinitz [3] examined the urine of thirty-five infants affected with gastro-enteric disorders. They concluded that the reducing action of the urine in such cases is always due, in part at least, to lactose. In a few cases they felt that they demonstrated the presence of galactose in addition to lactose. Contrary to Orban, they found that lactase was present in the intestinal contents of infants with

1. Grosz, J.: Jahrb. f. Kinderh. **34**:83, 1892.

2. Orban: Prag. med. Wchnschr. **24**:427, 441, 454, 1899.

3. Langstein, L., and Steinitz, F.: Beitr. z. Chem. Phys. u. Path. **7**:575, 1906.

glycosuria. They, therefore, concluded that the presence of lactose in the urine was not due to absence of lactase but was dependent on some intestinal injury which permitted the absorption of unchanged lactose.

During the past seven years I have examined the urines of infants affected with severe gastro-enteric or nutritional disorders with the object of determining the nature of the reducing agent when such was present. In the beginning, the urines were examined by practically every method which might elucidate the problem. As the work progressed, it became evident that many of the procedures were useless. It was found that an accurate determination of the nature of the reducing substance offered great difficulties owing to the small amount present in the urine and also in many cases to the diminished secretion of urine which is common in the gastro-enteric disorders of infants. Many of the available tests for the identification of sugars in dilute solution are inexact and uncertain when applied to urine containing less than 0.2 per cent. of sugar. This is generally true, but applies particularly to the identification of osazones and to polariscopic examination when only a small percentage of sugar is present. The fermentation test is inexact when the sole criterion is the formation of visible gas. Carbon dioxid is soluble to a degree in urine. The test, however, is of distinct value when used to determine whether the reducing substance is partly or completely destroyed by yeast with the formation of alcohol. In this manner, the test is useful even though the amount of sugar is too small to give rise to visible gas.

Before considering the tests to determine the nature of the reducing substance in the urine of infants with gastro-enteric disorders, it is necessary to consider briefly the question of urine sugar in general. For some time it has been considered probable that all normal urines contain reducing sugar. Recently Benedict and his collaborators [4] have shown that sugar is always present in the urine of normal adults and by means of fermentation with yeast can be divided into two fractions, one fermentable and one nonfermentable. They also found that the amount of urine sugar is dependent largely on the sugar intake. We have found that the same condition pertains to the urine of infants.[5] Since sugar is always present in normal urine, an estimate of its significance must be made on a quantitative basis. The presence or absence of reduction of copper test solutions is not sufficient, as such tests are purely qualitative and may be misleading. If the secretion of urine is less than normal, it can contain sufficient sugar to reduce a copper

4. Benedict, S. R.; Osterberg, E., and Chenowith, I.: J. Biol. Chem. **34**: 217. 1918.
5. Unpublished results of Dr. E. Harrington and myself. Also Greenthal, R. M.: Am. J. Dis. Child. **20**:556 (Dec.) 1920.

test solution and yet the total sugar eliminated may be abnormally small. Reversely, if there is diuresis, the total sugar elimination may be increased in the presence of a negative qualitative test.

For this reason, as pointed out by Benedict,[4] the use of the term glycosuria in its generally accepted meaning is no longer accurate. It has been used to designate the reduction of a copper test solution with the idea that sugar was an abnormal constituent of urine and was detected in this manner Owing to the inaccuracy of the term glycosuria, Benedict has proposed the term glycuresis to designate an increased sugar elimination.

TABLE 1.—Determination of the Reducing Substance by the Quantitative Method of Benedict

Name	Age, Mos.	Diet*	Reducing Substance in Urine, Calculated As Glucose, per Cent.	Fermentation With Yeast for 24 Hours		
				Gas Pro-duction	Reduction of Benedict's Qualitative Reagent after Fermenta-tion	Nonferment-able Reducing Substance, Calculated as Glucose, per Cent.
A. T.	3½	P. M.	1.1	++	+	Too small to determine
J. A.	4	B. W.	0.95	0	—	Too small to determine
J. Q.	5	P. M.	1.8	++	+	Too small to determine
W. Z.	5	W.	0.6	0	—	Too small to determine
A. B.	6	P. M.	1.63	++	+	0.68
B. Y.	6½	P. M.	2.1	+++	+	0.72
T. J.	7	P. M.	0.63	0	—	Too small to determine
C. M.	8	P. M.	0 22	0	—	Too small to determine
N. C.	8	B. W.	1.16	++	+	Too small to determine
W. T.	8½	P. M.	0.19	0	—	Too small to determine

* The diets given were the ones given during the period of urine collection. P. M. = protein milk (Finkelstein's formula); B. W. = 2 per cent. barley water; W = water.

Eighty-two patients were observed, from whom 196 specimens of urine were examined. All of the patients were affected with severe nutritional disturbances characterized by diarrhea, refusal of food, vomiting or loss of weight. The greater number of patients showed the presence of toxic symptoms. The urine of sixty-three infants reduced Benedict's qualitative reagent. The amount of the reducing substance was determined in sixty-five specimens of urine from thirty-eight infants by Benedict's quantitative reagent, Bertrand's method or the micro-method of Benedict and Osterberg.[6] The amount of reduc-

6. Benedict, S. R., and Osterberg, E.: J. Biol. Chem. **34**:195, 1918.

ing substance calculated as glucose varied from 0.12 to 2.1 per cent. Some of the results are shown in Tables 1 and 2.[7]

. The glycosuria in these cases is of relatively short duration, so that repeated examinations of the reducing substances in the urine of the same patient is often impossible. As a rule, glycosuria occurs only during the period of acute illness, and the patient either succumbs or improves within a few days. With improvement, the glycosuria diminishes markedly and subsides. The duration of glycosuria varies greatly, but in most cases covers a period of from one to four days.

TABLE 2.—DETERMINATION OF THE REDUCING SUBSTANCE BY THE MICRO-
METHOD OF BENEDICT AND OSTERBERG

Name	Age, Mos.	Diet*	Reducing Substance in Ur'ne, Calculated As Glucose, per Cent.	Fermentation With Yeast for 24 Hours		
				Gas Production	Reduction of Benedict's Qualitative Reagent after Fermentation	Nonfermentable Reducing Substance, Calculated as Glucose, per Cent.
S. C.	3	P. M.	0.582	0	+	0.184
M. D.	3	P. M.	0.163	0	—	0.063
D. W.	4	P. M.	0.5.	0	+	0.192
N. T.	4½	B. W.	0.386	0	—	0.097
A. T.	4½	P. M.	0.479	0	—	0.106
T. J.	5	W.	1,267	++	+	0.410
B. W.	5	P. M.	0.534	0	+	0.146
A. Z.	5	P. M.	0.293	0	—	0.072
D. W.	6½	P. M.	0.736	+	+	0.214
P. J.	7	P. M.	0.496	0	—	0.076
B. D.	7	P. M.	0.638	0	+	0.180
W. M.	7	B. W.	1,347	++	+	0.430
A. E.	8	B. W.	0.920	+	+	0.215
F. J.	8½	W.	0.464	0	—	0.093

* The diets given were the ones given during the period of urine collection.   P. M. = protein milk (Finkelstein's formula); B. W. = 2 per cent. barley water; W = water.

The short duration of the sugar elimination in this variety of case is in marked contrast to the continuous glycosuria associated with the regular ingestion of large amounts of sugar. A consideration of the latter type will be the subject of a separate communication.

As shown in the tables, fermentation by yeast always caused a marked diminution or entire disappearance of the reducing substance. In only nine specimens, however, was there visible gas production. These were the ones which contained the largest amount of reducing substance. In order to estimate correctly the amount of the reducing substance destroyed by yeast, it is necessary to consider the delicacy of the tests used. The method of Benedict and Osterberg is sufficiently delicate to show that the reducing power is practically never completely destroyed by yeast. Copper reduction tests are much less delicate and will be negative in the presence of amounts of sugar easily demonstrable

7. These results are from infants showing the largest amounts of urine sugar.

by the method of Benedict and Osterberg. The relation is largely quantitative. As a rule, tests with Benedict's qualitative copper solution are positive when the amount of sugar (estimated as glucose) is approximately 0.1 per cent. This variation in the results obtained with the two methods is apparent by comparing Tables 1 and 2.

These results show definitely that the greater amount of the reducing substance is fermentable and, therefore, they do not agree with the observations of Grosz, Langstein and Steinitz and others who found that the reducing substance was not fermented by yeast. The fact that in my cases the reducing substance was largely destroyed by yeast, indicates definitely that it was not lactose. Whether the fraction of the reducing substance not fermented by yeast was lactose is impossible to say. I am aware of no facts which bear directly on this question. This substance is usually present in amounts too small to determine its nature by the ordinary tests. Moreover, it always occurs in normal urine. It is of interest that in a number of cases the urine after fermentation still reduced Benedict's qualitative reagent (Tables 1 and 2). It is possible that part of this reducing action may have been due to the presence of a small amount of lactose in addition to the usual nonfermentable sugar of urine. Definite tests bearing on this question were not made.

Additional evidence that the reducing substance is not lactose was obtained by preparing osazones from ten specimens of urine. These specimens all contained 1 per cent. or more of reducing substance calculated as glucose so that sufficient osazones were obtained for purification. Their solubility, appearance and melting point indicated that the sugar was not lactose but was probably glucose (Table 3).

TABLE 3.—APPEARANCE, SOLUBILITY AND MELTING POINT OF OSAZONES

Name	Percentage of Reducing Substance Calculated as Glucose	Appearance of Osazone	Melting Point of Osazone, Degrees C.	Solubility of Osazone in Hot Water
A. J.	0.962	Glucosazone	205.6	Not perceptably soluble
T. P.	1.1	Glucosazone	203.8	Not perceptably soluble
W. A.	1.3	Glucosazone	204.0	Not perceptably soluble
T. J.	0.873	Glucosazone	204.6	Not perceptably soluble
O. M.	1.6	Glucosazone	205.0	Not perceptably soluble
J. W.	1.25	Glucosazone	206.2	Not perceptably soluble
W. S.	0.92	Glucosazone	206.0	Not perceptably soluble
O. W.	1.4	Glucosazone	205.2	Not perceptably soluble
F. A.	0.775	Glucosazone	205.8	Not perceptably soluble
A. L.	0.18	Glucosazone	204.4	Not perceptably soluble

The fact that the main portion of the reducing substance is fermentable indicates that it is glucose or galactose. The speed with which fermentation occurs points to the former. Galactose is fermented by yeast but more slowly than glucose. Definite data bearing on this

question were obtained in six cases. In these the urine contained more than 1 per cent. of reducing substance calculated as glucose. Quantitative determinations by means of Bertrand's method were compared with the rotation of polarized light. The values always corresponded much more closely with the specific rotation of glucose (52.5) than with galactose (81). For example: a specimen of urine gave a copper precipitate which was equivalent to 2.12 per cent. glucose. Calculated as galactose the percentage was 2.14 per cent. In a 2 decimeter polarimeter tube the rotation was 2.02 degrees, which calculated as glucose was equivalent to 1.92 per cent. sugar. Calculated as galactose the percentage was 1.24.

TABLE 4.—INFLUENCE ON URINE SUGAR OF CHANGE OF DIET FROM PROTEIN MILK TO WATER. URINE COLLECTED FOR PERIOD OF 8 HOURS AND SUGAR OUTPUT FOR 24 HOURS CALCULATED FROM THIS

Name	Protein Milk Sugar Output, Mg. per 24 Hours Calculated as Glucose	Water Sugar Output, Mg. per 24 Hours Calculated as Glucose
Gerald	640*	128*
Ellwood	506*	420*
Miller	610†	615†
Geyer	395*	340*
Cerecle	820*	195*
Kroph	560†	470†
Ratchfod	718†	230†
McLean	483†	406†
O'Neil	540*	204*
Lunetti	762†	607†
Smith	491†	602†
Peny	480*	163*
Barrows	623*	201*
Kintas	380*	350*
Miller	963*	770*
Sweney	820	695*

* Determined by micro-method of Benedict and Osterberg.
† Determined by the quantitative copper solution of Benedict.

The results of these determinations also offer additional evidence that the reducing agent was not lactose. Using the example cited, if the reducing action of the urine was due to lactose, the percentage would have been about 2.9. Calculated by the rotation, the percentage of lactose would have been 1.29. The mucic acid test was applied to these urines with uniformly negative results.

In addition to the chemical evidence there are a number of clinical observations which have a direct bearing on the nature of the reducing substance. If this substance is lactose or galactose it should be present in the urine only when lactose is ingested. This is not the case. Six infants with severe nutritional derangement (intestinal intoxication), whose urine showed marked reducing action, had received water or barley water alone for from sixteen to twenty-four hours.

Sixteen infants whose urine exerted a marked reducing action on copper solutions while receiving protein milk (Finkelstein's formula) as food were given water alone for from ten to eighteen hours. In six cases the reducing power of the urine was markedly decreased. In ten cases a quantitative determination showed only slight diminution of the reducing action of the urine (Table 4).

In consideration of these clinical tests alone, it seems inconceivable that the reducing action of the urine was due to lactose. No lactose was ingested and so far as is known the infant organism is incapable of storing or synthetizing lactose. On the basis of such evidence it seems that the reducing agent could only be glucose, the sugar of the body fluids.

While the results cited seem to warrant the conclusion that the reducing action of the urine of infants with nutritional disorders of the type observed is due to glucose and not lactose, it is not my intention to imply that alimentary lactosuria does not occur. Most of the patients on whom my investigations were conducted received food containing little lactose. This may perhaps explain to some degree the difference in my results and those of Grosz, Orban, Langstein and Steinitz and others.

In my experience, lactosuria has occurred only in infants who were not thriving and who were ingesting considerable lactose. The following case will serve as an example.

REPORT OF CASE

Baby F., aged 3 months, received in twenty-four hours 28 ounces of a milk and whey formula containing about 12.5 per cent. lactose. Just preceding a nutritional disturbance, the urine reduced Benedict's qualitative reagent, and a quantitative determination by Bertrand's method showed a reducing power equivalent to 1.95 per cent. glucose. Incubation with yeast for twenty-four hours showed no gas formation, and a second quantitative determination showed only a slight diminution of reducing power, a glucose equivalent of 1.58 per cent. After hydrolysis with 1 per cent. hydrochloric acid incubation with yeast for twenty-four hours caused distinct gas formation and a marked impairment of reducing action. Quantitative determination after fermentation for thirty hours showed an equivalent of about 0.3 per cent. glucose. The osazone had the appearance of lactosazone and dissolved almost completely in hot water.

These results would seem to indicate that the greater portion of the reducing substance was lactose although there was also in all probability a small amount of glucose. Similar results were obtained in the case of six other infants who were receiving moderate or large amounts of lactose in their food.

During investigations of lactose tolerance, lactosuria occurred in three cases. These cases, however, were exceptional. As a rule, when the urine reduced Benedict's qualitative reagent following the ingestion

of large amounts of lactose it was due to a readily fermentable sugar which was apparently glucose.

Infants with severe nutritional disorders usually secrete much less urine than normal which in consequence is concentrated. The question naturally arises whether the reduction of copper solutions by the urines of these patients actually represents an increased sugar output. Since normal urine always contains reducing sugar, it seems possible that with diminished urine secretion the concentration of sugar may be sufficient to reduce copper solutions without there being an actual increase in the amount of sugar eliminated. There seems little question that the increased concentration of the urine may be a factor in the frequency with which such urines reduce copper test solutions. If this were the only factor concerned, there might be only an increase in the percentage of urine sugar but no true glycuresis.

TABLE 5.—Comparison of Sugar Output in Urine During Period of Acute Symptoms and After Recovery. Urine Collected for a Period of 8 Hours and the 24-Hour Output Calculated from This

Name	Period of Acute Symptoms		After Recovery	
	Protein Milk, Amount Ingested in 24 Hours, Ounces	Sugar per 24 Hours as Glucose, Mg.	Food, Ounces	Sugar per 24 Hours as Glucose, Mg.
Ellwood......................	9	506	Milk......... 11 Lactose..... ½	206
Cerecle......................	7	820	Breast milk. 14	180
Lunetti......................	16	762	Protein milk 23 Maltose..... 1	207
Kinetas......................	2	380	Milk......... 14 Lactose..... ½	240
Miller......................	8	963	Protein milk 13 Cane sugar.. ½	193

Evidence on this question is given by quantitative determination of the total sugar output. Such determinations were made on the urine voided during eight hours, and the twenty-four hour elimination was calculated from this period. The total sugar per twenty-four hours calculated in this manner ranged from 280 to 963 mg. Some of the results are shown in Table 4. These figures indicate a greatly increased sugar elimination as normal infants on such a restricted sugar intake rarely put out more than 150 mg. Sugar eliminations comparable to these are found in normal infants only when very large amounts of sugar are ingested. Additional evidence was obtained in five cases in which the sugar output during the period of acute symptoms was compared with that after recovery. Despite the much greater sugar ingestion after recovery the sugar output was much less (Table 5). It,

therefore, seems evident that infants with nutritional disorders may show a true glycuresis.

Finally, the origin and significance of the increased sugar output must be considered. Is it due to a disturbance of sugar metabolism or is it merely of renal origin? Blood sugar determinations have been made in sixteen cases, and in all but two there was distinct hyperglycemia. The blood sugar after four hours' fasting ranged from 140 to 210 mg. per 100 c.c. This would seem to indicate a disturbance in the metabolism of sugar rather than the presence of a purely renal glycuresis. Increased blood sugar in the presence of increased urine sugar is generally assumed to indicate a disturbance in sugar metabolism.

As to the ultimate cause of the glycuresis, there is no direct evidence on which to base a definite opinion. There are a number of general observations on sugar metabolism which might have a bearing on this particular subject and which open a tempting field for discussion. It is my belief, however, that such discussion would go but a little way toward elucidating the problem and should be deferred until evidence bearing directly on the subject is available.

A PECULIAR FEVER OF INFANCY, PROBABLY DUE TO DEPLETION OF THE WATER RESERVE OF THE BODY *

C. G. GRULEE, M.D., AND B. E. BONAR, M.D.

CHICAGO

The following observations were made at a time when we were very much interested in the subject of fever in infants, which we were studying from another standpoint. The idea advanced by Balcar, Sansum and Woodyatt [1] that there might be a direct connection between a reduction of the water content of the body and the occurrence of fever is one which is especially attractive and probably can best be demonstrated, if at all, in the period of infancy. Most of the support from the literature which the theory has obtained has come from observations made on infants. It has, therefore, seemed to us that a report of some of our cases might be of interest.

REPORT OF CASES

CASE 1 (No. 132697).—George G., aged 2 months, entered the Presbyterian Hospital Feb. 15, 1920. The complaint was vomiting and undernourishment.

History.—The child was born by forceps delivery with a birth weight of 7¾ pounds. Pregnancy had been normal. He was put to the breast but did not nurse well and was fed breast milk with a spoon for some days. After two weeks he was given a mixture of 9 ounces of certified milk, 6 ounces of water, 2 teaspoonfuls of dextrimaltose and 20 drops of milk of magnesia. This was later increased to 10 ounces of milk, 18 ounces of water, 1 level teaspoonful of dextrimaltose, and 4 teaspoonfuls of milk of magnesia. For four days previous to entrance he had been given Horlick's malted milk. The day before entrance certified milk was again tried.

The child had never regained its birth weight and vomited practically everything. The type of vomiting was almost projectile. Vomiting became worse. The bowels had been regular, urination regular, the child slept soundly and was good natured. The bowel movements at times had been full of curds and sometimes were loose. There had been no convulsions or spasms.

Family History.—The family history was negative. This was the only child; there had been no other pregnancies. The father and mother were alive and well.

Physical Examination.—On physical examination there was found to be a poorly nourished infant who gave the impression of being very sick. The head was rather large; the fontanel was open; a slight nasal discharge was present; the face was pale and rather emaciated; no skin lesions were noted. The cervical and auricular glands were palpable; the neck was held back but no spasticity was noticed. Lungs and heart were negative; abdomen was distended. No peristalsis was noted at this time, fifteen minutes after taking nourishment,

although the stomach was well outlined and there was some movement, but this was not a distinct peristalsis.

February 16, the von Pirquet reaction was negative.

February 17, the child vomited most of its food but seemed to retain enough not to lose weight.

February 18, the baby was rather constipated and still vomited.

February 19, peristaltic waves were seen passing over the stomach and there was projectile vomiting.

February 20, this peristalsis was much more marked as was also the vomiting which was definitely projectile.

Roentgen-ray examination indicated retention of food in the stomach; the stools were hard.

An exploratory laparotomy was done under local anesthesia but no tumor was found and the abdomen was closed.

February 21 and 22 the vomiting was still, marked.

February 22, a continuous enema of 6 per cent. dextrose solution was given. This was continued through the twenty-third and the twenty-fourth.

February 25 the child began to retain food.
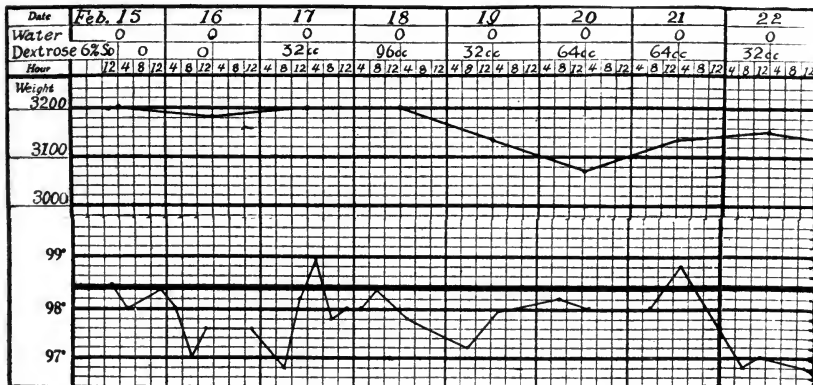
Fig. 1.—George G.; prefebrile period. Food: Albumin milk, 576 c.c.; dextri-maltose, 24 gm. Six feedings of 96 c.c. each.

February 28, 55 c.c. of a 6 per cent. solution of dextrose was given subcutaneously.

Clinical Course.—The course of this case so far as temperature was concerned may be divided into the prefebrile period, the febrile period, and the postfebrile period. The prefebrile period extended from February 15 to February 23. During this time the child obtained as food 18 ounces (576 c.c.) albumin milk; ¾ ounce (24 gm.) dextrimaltose, six feedings of 3 ounces (96 c.c.) each. During this period there was no rise in temperature. The child received 6 per cent. dextrose solution, three times a day, beginning with the seventeenth. The child obtained from 1 to 5 ounces a day of this solution (32 to 160 c.c.). February 18, atropin sulphate, $\frac{1}{1,000}$ grain, was administered hypodermically every eight hours. This was discontinued on the twenty-third. The stomach was washed before each feeding; this, too, was discontinued on the twenty-third.

The second period is the febrile period, which lasted from February 23 to March 7. During this time the child received food consisting of 8 ounces (256 c.c.) whole milk, ¾ ounce (24 gm.) dextrimaltose, 1 ounce (32 gm.) flourball, to which 8 ounces (256 c.c.) of water was added and the whole boiled
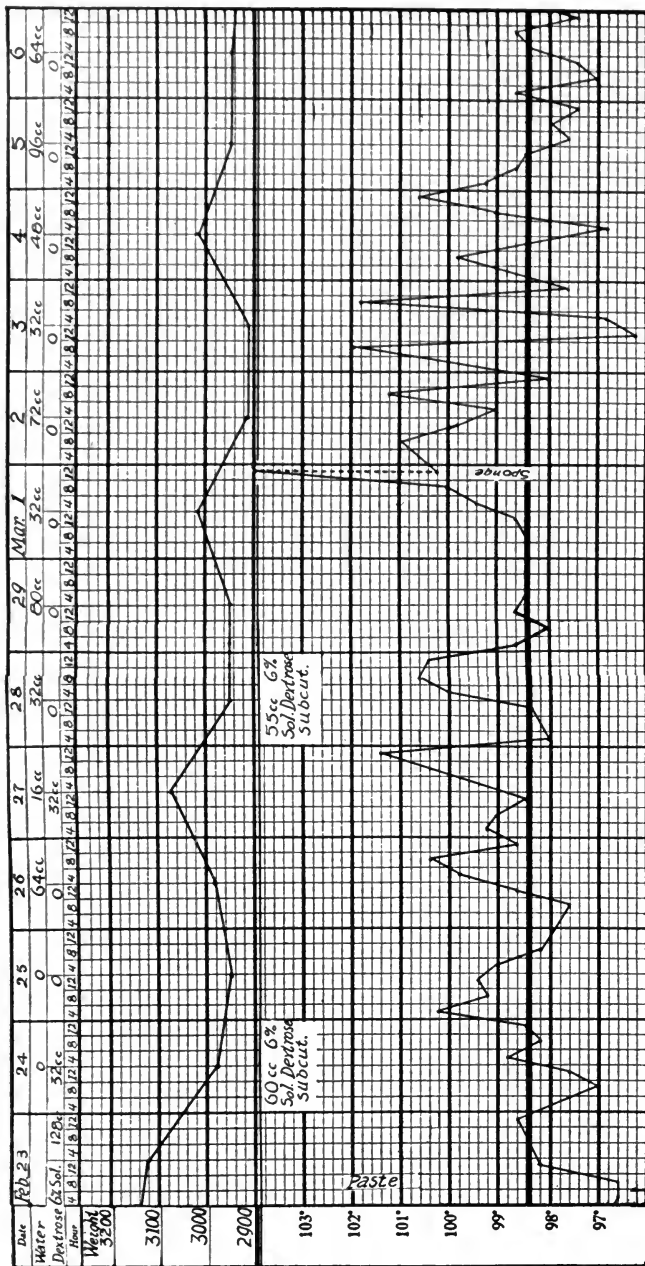
Fig. 2.—George G.; febrile period. Food: Paste made from whole milk, 256 c.c.; dextrimaltose, 24 gm.; flourball, 32 gm.; water, 256 c.c.

down to a thick paste. Atropin was given, $\frac{1}{1,000}$ grain, every four hours; strychnin, $\frac{1}{1,000}$ grain, three times a day, both being given hypodermically. An attempt was made to give dextrose solution by the drop method rectally but without much success because the child retained very little of it. The strychnin was discontinued on the third, and on that day the atropin was ordered given only twice a day. Only small quantities of water were given at this time, varying in twenty-four hours from 16 to 96 c.c. February 28, the child was given 55 c.c. of 6 per cent. dextrose solution subcutaneously.

The third or postfebrile period began March 7 and continued through to the twenty-third. During this period the paste was gradually replaced, one feeding at a time, with liquid, consisting of 2 ounces (64 c.c.) milk, and ¼ ounce (8 gm.) dextrimaltose. The first of these feedings was given March 7. March 15 two feedings were given; on the seventeenth three feedings, and from the nineteenth on all feedings were of liquid nourishment.

During this last period the temperature exceeded 99 F. three times. On the afternoon of March 8, after the child had shown a subnormal temperature, dropping following liquid nourishment, the temperature rose to 100.8 F., dropping immediately to 96.6 F. On the following afternoon, March 9, the temperature rose to 99.4 F., and on the afternoon of the twentieth the temperature at one time registered 99.6 F. With these exceptions, this period was in marked contrast to the period when the child received only a thickened paste. Throughout the treatment the child refused water, the total daily quantity never exceeding ½ ounce (16 c.c.). The urine was negative on several examinations. February 16, the blood showed: Erythrocytes, 4,500,000; leukocytes, 7,500; hemoglobin, 75 per cent. Differential count: Small lymphocytes, 56 per cent.; polymorphonuclears, 44 per cent.

Comment.—Practically the only difference between the second period and the first and third periods consisted in the fact that the quantity of water which the child took was very much reduced in the former. There was no other circumstance which was clinically evident which we could in any way connect with a rise in temperature. It should be remembered that this was an extremely emaciated infant, as the weight curve shows, that it had been subjected to a long period of reduction by vomiting, and that, hence, in all probability the water content of the body was greatly reduced.

CASE 2 (No. 133045).—Mary Z., aged 6 months, entered the Presbyterian Hospital, Feb. 27, 1920.

History.—Born spontaneously with a birth weight of about 7 pounds. Breast fed for five months during which time her general condition was good. One month before entrance, the child had a cold and a slight cough. During the daytime the child had been vomiting. Its food at the time of entrance had been four feedings of cow's milk, three parts milk to one of water, with two teaspoonfuls of sugar per bottle, in addition to which had been given one cereal and one vegetable feeding. The child was apparently doing well, although there was a history of some vomiting. Two days before entrance the mother had noticed some discharge from the ear. Previous to this time the child had had no disturbance of any sort. Mother stated she was easy to take care of, took her food eagerly and slept well.

Family History.—This was the sixth child, the oldest being 14 years of age. Two miscarriages; children all apparently well; father alive and well. The mother soon after the entrance of the child into the hospital was taken to an insane asylum because of dementia praecox.

Physical Examination. — This revealed nothing abnormal, except that the child was poorly nourished, weight about 10 pounds. There was a somewhat
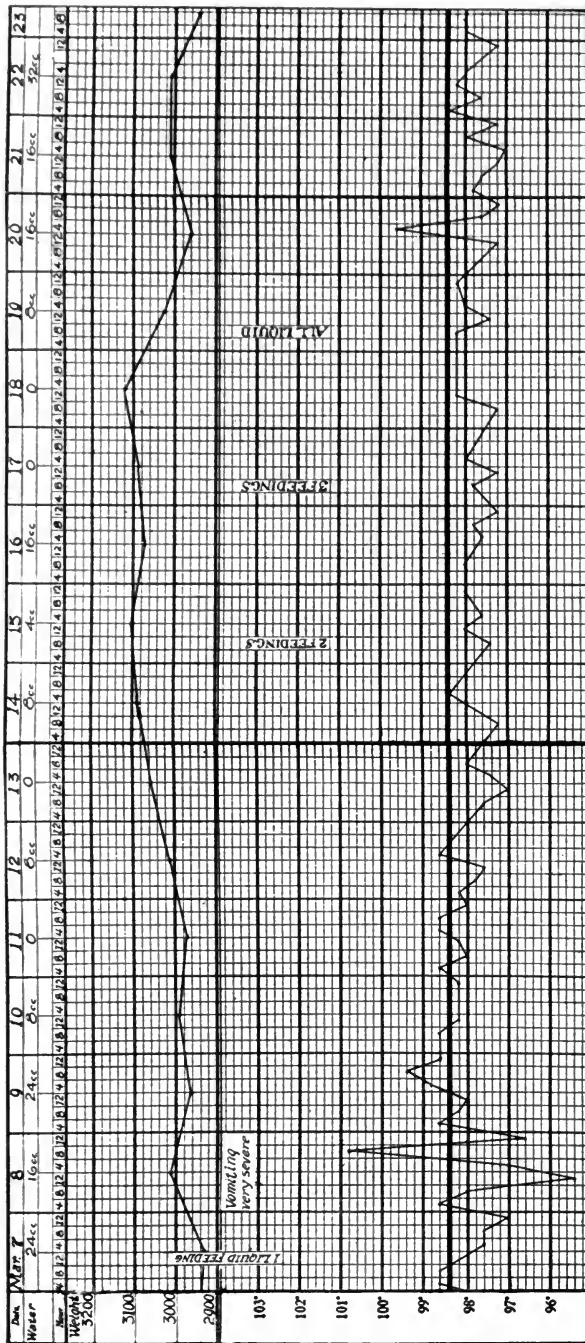
Fig. 3.—George G.; postfebrile period. Food: Each liquid feeding consists of whole milk, 64 c.c.; dextrimaltose, 8 gm.
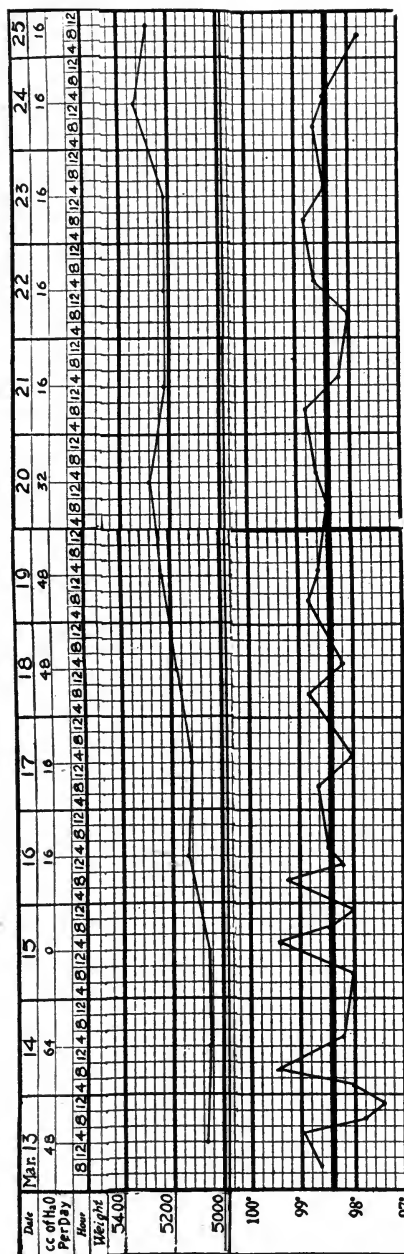
Fig. 4.—Mary Z. First period. Food, March 13: Albumin milk, 1,056 gm.; dextrimaltose, 32 gm. Five feedings of 224 c.c. each.

purulent discharge from the right external auditory meatus. Other physical findings were negative.

The discharge from the ear ceased March 3 and never recurred thereafter. During the early days of the child's stay in the hospital its food consisted of 30 ounces (960 c.c.) albumin milk; 1 ounce (32 gm.) dextrimaltose, five feedings of 6 ounces (192 c.c.) each. This was increased to 33 ounces (1,056 c.c.) albumin milk; 1 ounce (32 gm.) dextrimaltose, five feedings of 7 ounces (224 c.c.) each on the ninth. Although the child had been vomiting more or less throughout its stay in the hospital, rumination was first actually noticed March 22, and the food was not changed until March 25.

Clinical Course.—From the time of its entrance to March 25 constitutes the first period in our history. During this period the temperature was nearly always within normal limits. March 2 it rose once to 99.4 F.; March 10 it rose once to 100 F.; March 11 it rose once to 99.6 F., and once to 99.2 F. March 14 the temperature was 99.6 F. once; March 15, 99.6 F. once; March 16, 99.2 F. With these exceptions, the temperature from February 27 to March 25, in all twenty-eight days, never rose above 99 F. During this first period, in addition to the food, the child obtained some water between feedings.

As medication during this first period, from March 13 to March 24, the child received a teaspoonful of cod liver oil and phosphorus twice a day. March 24 this was increased to three times a day and remained the same throughout the course. March 24 the child was given $\frac{1}{1,000}$ grain atropin hypodermically, every four hours, and this was kept up for two days when the dose was reduced to $\frac{1}{2,000}$ grain and this was continued until March 30.

The second period began March 25. The child was given food consisting of 15 ounces (480 c.c.) whole milk, $\frac{1}{2}$ ounce (16 gm.) dextrimaltose, $1\frac{1}{2}$ ounces (48 gm.) cream of wheat, the whole boiled down to a paste and given in five feedings. March 26 this was increased to 18 ounces (576 c.c.) milk, $\frac{1}{2}$ ounce (16 gm.) dextrimaltose, and 2 ounces (64 gm.) cream of wheat. March 28 this was still further increased to 20 ounces (640 c.c.) whole milk, $\frac{3}{4}$ ounce (24 gm.) dextrimaltose and 2 ounces (64 gm.) cream of wheat. This latter feeding was continued until May 3.

Beginning the afternoon of March 26, the temperature became irregular and remained so until the afternoon of May 3. During this time the quantity of water consumed was very low. The only days when the temperature was within normal limits were April 3 and 4. On these two days the quantity of water given was not in excess of that consumed in the other period.

The third period began May 3. At that time the child was given 20 ounces (640 c.c.) milk, $\frac{3}{4}$ ounce (24 gm.) dextrimaltose, 20 ounces (640 c.c.) water, five feedings of 8 ounces (256 c.c.) each. On the afternoon of May 3 the temperature showed a sudden drop to normal. May 4 in the afternoon the temperature dropped to 95.2 F. and the child was in a state of collapse. The Intern became alarmed and ordered that the child be put again on thick cereal feeding. The condition was so alarming that the child was given camphorated oil, 8 minims, and strychnin sulphate, $\frac{1}{500}$ grain, hypodermically. This was continued for two further doses and early in the morning of May 5 it was necessary again to give the child 8 minims of camphorated oil. When the child was seen by the attending man next morning, the liquid food was again ordered and by noon the temperature had dropped to 97.8 F., and in the afternoon it fell to 96.4 F.

This feeding was continued until May 10. The temperature became markedly subnormal; on the eighth it rose to 99.4 F., then dropped to 96 F.; on the ninth, it dropped to 96 F.; the morning of the tenth it again rose to 99.4 F., and dropped to normal that afternoon.

In the fourth period, beginning May 10, the child was again put on the paste consisting of 20 ounces (640 c.c.) whole milk, $\frac{3}{4}$ ounce (24 gm.) dextrimaltose, 1 ounce (32 gm.) cereal in five feedings. This was continued until
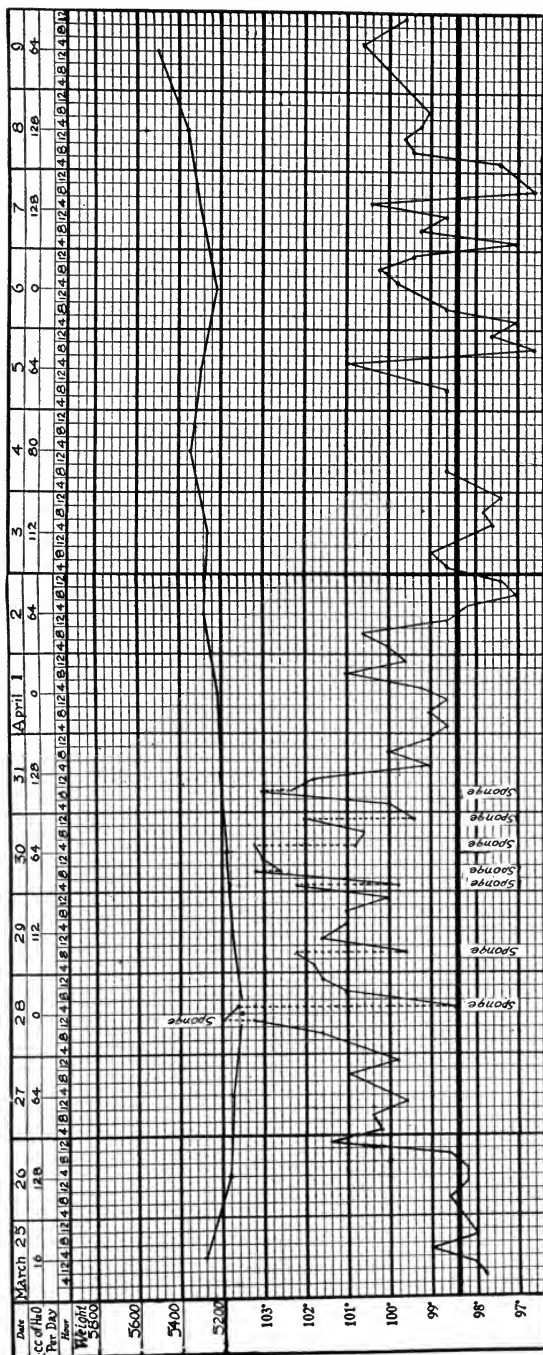
Fig. 5.—Mary Z. Second period. Food, March 25: Paste consisting of whole milk, 480 c.c.; dextrimaltose, 16 gm.; cream of wheat, 48 gm. March 26-28: Paste consisting of whole milk, 576 c.c.; dextrimaltose, 16 gm.; cream of wheat, 64 gm. March 28 to May 3: Paste consisting of whole milk, 640 c.c.; dextrimaltose, 24 gm.; cream of wheat, 64 gm.
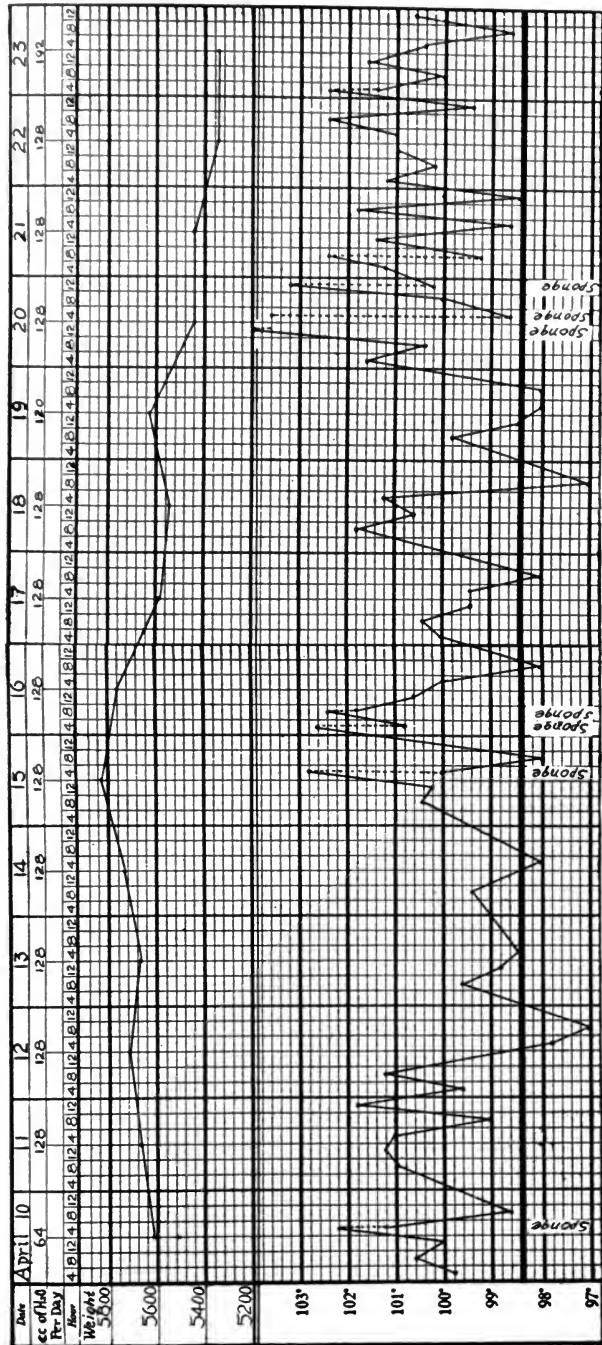
Fig. 6.—Mary Z. Second period (continued). Food: Same.

the fifteenth. During this period the child again showed a markedly febrile temperature.

May 15, when the fifth period began, the child was put on food exactly the same as during the previous period (fourth), except that 20 ounces (640 c.c.) water was added and the whole was not made into a paste, and five feedings of 8 ounces (256 c.c.) each were given. The afternoon of May 15, the child again showed a marked drop in temperature, 96.4 F. This was followed by a slight rise to 100.6 F. the next day. The child was perspiring very freely. The temperature dropped to 96.4 F. on the seventeenth and remained low.

May 25 the food was again changed (sixth period), the same food being given as during the fourth period. The afternoon of May 25, the temperature rose to 101 F. and on the twenty-sixth it rose to 101.6 F. It was decided then to push water, and the quantity, which for the previous ten days had varied between 32 and 96 c.c. per day, was increased so that the following quantities were given:

May 26.....................	304 c.c.	May 31.....................	384 c.c.
May 27.....................	400 c.c.	June 1.....................	328 c.c.
May 28.....................	208 c.c.	June 2.....................	320 c.c.
May 29.....................	308 c.c.	June 3.....................	448 c.c.
May 30.....................	288 c.c.		
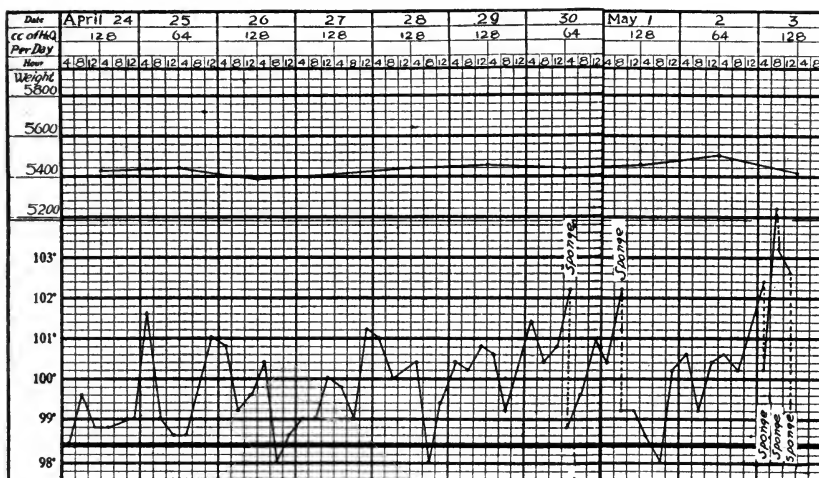
Fig. 7.—Mary Z. Second period (continued). Food: Same.

The afternoon of the twenty-sixth, the temperature dropped to normal; on the twenty-seventh it was subnormal; on the twenty-eighth it was normal. It was slightly above normal on the twenty-ninth, and the afternoon of the thirtieth it began to rise. From then on until June 3, the temperature remained somewhat high, though lower than in the previous period.

June 3 (seventh period), the food was again changed back to that of the fifth period. The temperature on the fourth dropped to 95.2 F. and remained subnormal with one exception until the fourteenth. On the ninth the temperature rose once to 101 F. This was a hot, humid day.

The quantity of water consumed during this period varied between 64 and 272 c.c.

During the next period (the eighth) from June 14 to June 25, the same food was given as in the sixth period. June 15, the temperature rose to 101 F., but with the administration of water, 400 c.c. June 16, 336 c.c., and the seventeenth, 360 c.c. water were given and the temperature remained

down. Water was restricted on the seventeenth so that the child after that received for this period no more than 96 c.c. per day, with the result, that the remaining part of this period the child ran a febrile temperature throughout.

June 24 (ninth period), the child was again put on a liquid food of the same composition as during the seventh period. That evening, the temperature dropped to 97.2 F., remaining subnormal for three days thereafter, being within normal limits until the end of this period, July 2.

Comment.—The difference in temperature bore such direct relation to the water intake throughout this case that we decided to see if it were possible to obtain any confirming evidence by blood examination. For this purpose there were made careful estimates of the number of red and white cells, the hemoglobin, and the specific gravity. The specific gravity was estimated by the benzol-chloroform method, the specific gravity of the liquid being carefully estimated by means of a Westphal balance.

Blood Examination.—The blood examination in each instance was made at 10 a. m., one hour after the ingestion of food.

TABLE 1.—Blood Findings in Case of Mary Z. During Sixth Period While the Child Was on Liquid Nourishment

Date	Hemoglobin	Erythrocytes	Leukocytes	Sp. Gr. at 16 C.
6/10/20................	85%	4,790,000	6,700	1.056
6/11/20................	85%	4,864,000	7,650	1.052
6/12/20................	90%	4,998,000	8,600	1.062

TABLE 2.—Blood Findings in Case of Mary Z. During the Seventh Period When the Child Was on Food Paste

Date	Hemoglobin	Erythrocytes	Leukocytes	Sp. Gr. at 16 C.
6/19/20................	95%	5,300,000	9,980	1.072
6/20/20................	92%	5,460,000	9,700	1.069
6/21/20................	95%	5,330,000	9,000	1.070

Comment.—If we may regard the recent observations of Wimberger [2] as conclusive, this observation of the difference in the concentration of the blood is quite remarkable in that in his observation on children between 7 months and 17 years of age, he found that the variation in the volume of the blood serum was extremely small, and he thinks that the blood is independent of the water content of the surrounding tissues, even in very marked changes in weight.

When we stop to consider the cause of fever in these cases, we naturally revert to the various theories which have been advanced as the reason for the increase of temperature in the human body. These may be placed into three groups: (1) Fever due to some involvement of the central nervous system; (2) fever of an infectious or bacterial origin, and, (3) dehydration fever. In neither of the cases here

2. Ztschr. f. Kinderh. **25**:64, 1920.

reported need we consider the question of fever caused by some derangement of the central nervous system. There was certainly nothing of that nature in either of the cases. Therefore, we must be confined in our discussion to the last two causes; namely, bacterial and dehydration.

The question that arises in both these cases is whether or not the changed conditions from the removal of water from the food are responsible for an absorption of bacteria from the intestine with a resulting bacterial infection and toxemia. We may certainly dismiss from our discussion any other source of bacterial infection, and we

Fig. 8.—Mary Z. Third period. Food: Whole milk, 640 c.c.; water, 640 c.c.; dextrimaltose, 84 gm. Five feedings of 256 c.c. each.

think it fair to assume that there is a very definite connection between the giving of thickened food and the rise of temperature, since in both cases there is evident such a definite time relation between the two conditions, the temperature falling quite evidently as the result of the giving of liquid food. While it would be impossible to state absolutely that there was no bacterial infection, or absorption of dead bacterial bodies under the circumstances above mentioned, still there are many points which speak very decidedly against such a condition. In the first place, although the temperature curve, especially in Case 2, lasted over many weeks, there was at no time any evidence of

toxemia.   The child was somewhat disturbed by thirst, but no general
symptoms of toxemia or septicemia such as are regarded as character-
istic of these conditions were to be observed in the child.   In the second
place, if such infectious conditions did occur, we would certainly
expect that there would be shown some evidence of involvement of
the gastro-intestinal tract.   In conditions due to bacterial infection
from the gastro-intestinal tract, or to toxemia produced by conditions
within the gastro-intestinal tract, the gastro-intestinal symptoms are
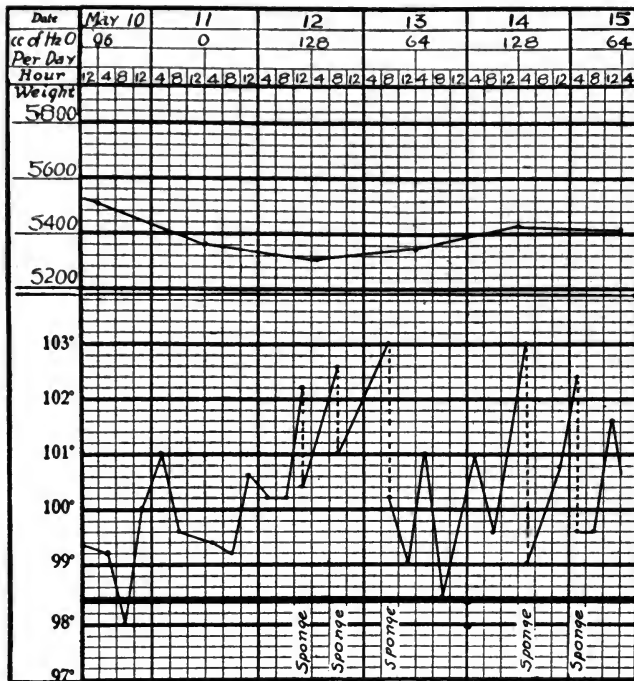
Fig. 9.—Mary Z. Fourth period. Food: Paste consisting of whole milk,
640 c.c.; dextrimaltose, 24 gm.; cream of wheat, 32 gm.

practically always in proportion to the height of the temperature.   In
other words, when temperature elevation depends on a gastro-intes-
tinal disturbance, the number of stools is increased and the character
of the stools is changed to a much greater degree than if that same
temperature is produced by an infectious process which does not refer
to the gastro-intestinal tract.

Diarrhea was not present in either of these cases at any time, nor
was there any perceptible change in the character of the stool, no
matter whether the child was on the liquid or the solid food. We
may, therefore, say that while we cannot absolutely rule out bacterial
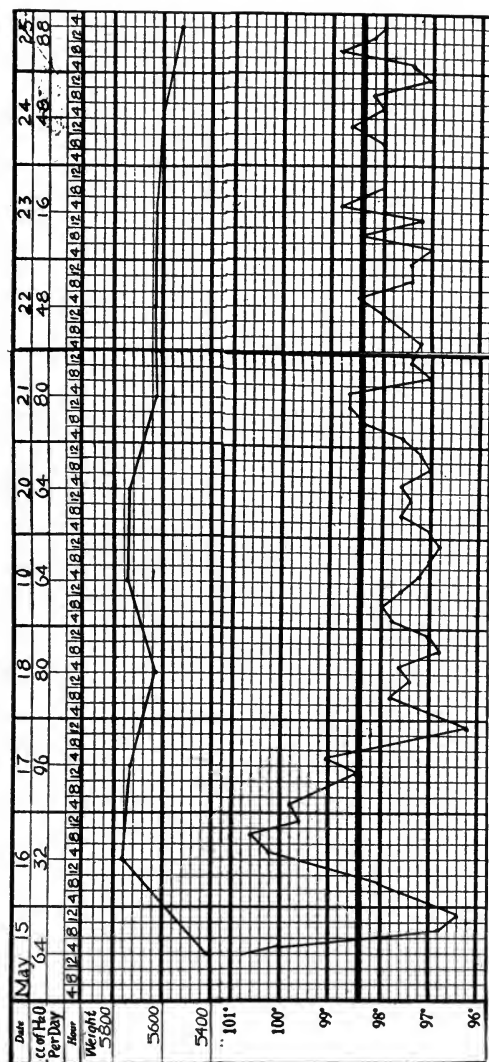
Fig. 10.—Mary Z. Fifth period. Food: Whole milk, 640 c.c.; dextrimaltose, 24 gm.; cream of wheat, 32 gm.; water, 640 c. Five feedings of 25 c.c. each.

Fig. 11.—Mary Z. Sixth period. Food: Same as in fourth period.
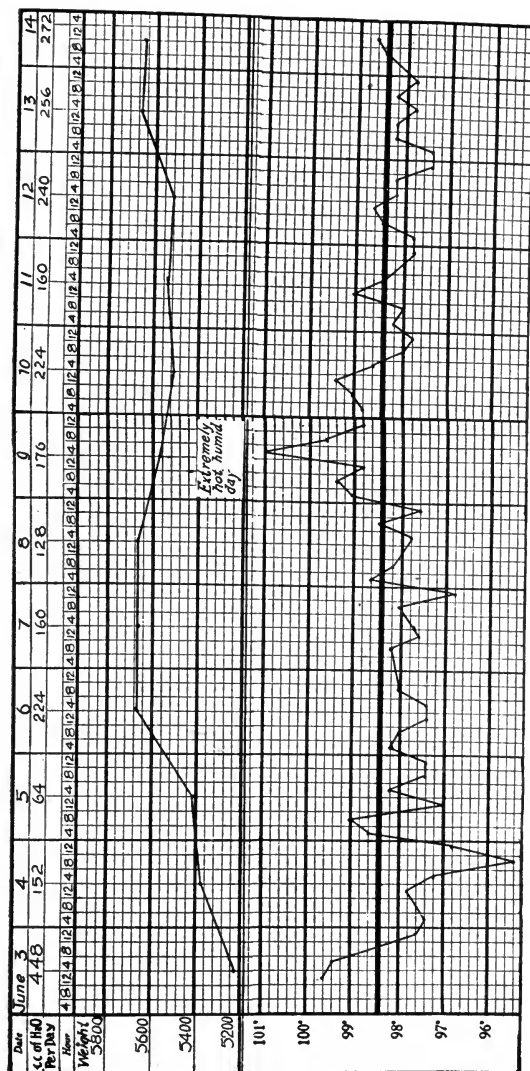
Fig. 12.—Mary Z. Seventh period. Food: Same as in fifth period.

infection in this instance, all clinical signs point very strongly against such an element entering into the explanation of this fever.

In considering the third cause of fever, dehydration, many points in both these cases, but especially in Case 2, favor such an explanation. First, there is the very definite increase of temperature within a short time after the beginning of the thick paste feeding. Second, there is the continuation of this fever throughout the entire time when the paste is being given. Third, this fever ceases very shortly after the child is put on liquid food. Fourth, for a certain length of time while the child is on thickened food this fever may be reduced by the introduction of large quantities of water by mouth. Fifth, there is distinct evidence of a difference in the water content of the blood between the period of liquid feeding and that of thickened feeding, the blood being much more highly concentrated during the latter than during the former period.

It seems likely that the water content of the body exists really in three forms; available water, residual water and essential water. If we accept the dehydration theory of fever, and apply it to these cases, it would seem likely that in both cases, due not to malnutrition but to undernutrition caused by the rejection of food through vomiting and rumination, the system of each of these infants had lost any surplus which the body might have contained had these processes not been present. When the paste food was given, therefore, there was withdrawn from the body for the purposes of digestion a rather large quantity of water. The withdrawal of this water resulted in a dehydration, with consequent rise of temperature. When the digestive processes were completed, this water could again be absorbed, with the result that an up and down temperature curve would be produced. That the margin is very narrow may readily be seen by the quantity of water which is sufficient to reduce this temperature. A difference of from 150 to 200 c.c. a day was sufficient to produce a cessation of the fever, at least temporarily. In the first case, too, there was a very definite change soon after the first liquid feeding was given, although the quantity of fluid was very small.

One phenomenon occurred in the last case which we are not able to explain satisfactorily at present, and that is the acute collapse which occurred when liquid food was given following a period of thickened food. It is interesting to note that the collapse was most severe following the prolonged use of the thickened food, and was less marked when the thickened food had been used only a short time. There seemed, however, to be that tendency after each period of thickened food nourishment. The only clinical picture which we know of that corresponds to that seen in these cases is the acute collapse
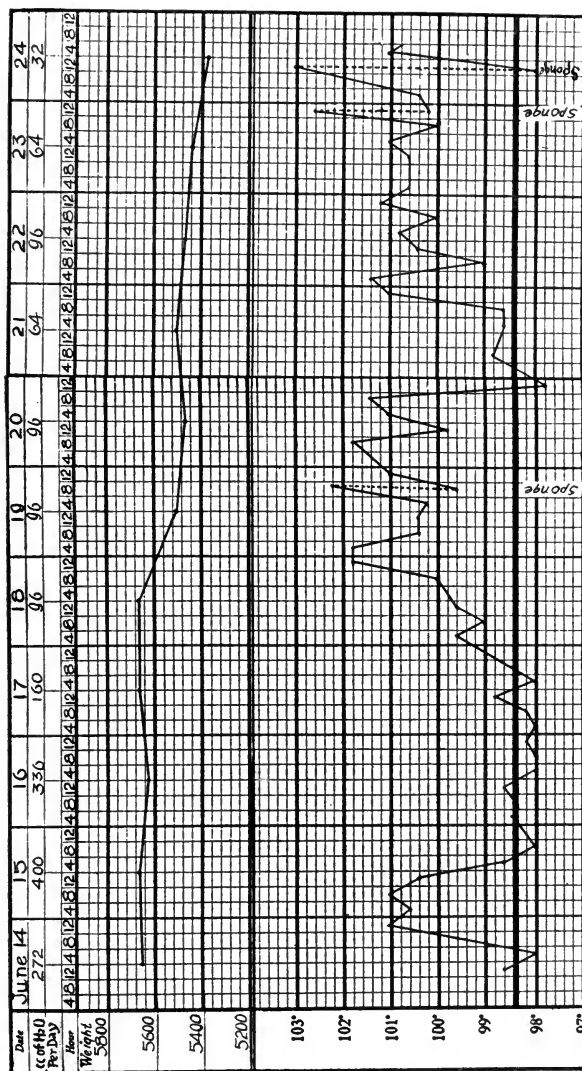
Fig. 13.—Mary Z. Eighth period. Food: Same as in sixth period.

sometimes seen in severely marantic infants. Whether these two conditions are identical or not it would be impossible to say.

The practical importance of these observations suggests itself at once. Fevers of unknown origin have always been described in infancy. There have also been described fevers whose explanation was certainly inadequate; such, for instance, as the temperatures which have been described during teething. Such fevers might possibly, if properly analyzed, fall into a group like that described in this paper. It should be noted, however, that such fevers are to be described only under certain conditions and those conditions must correspond to a dehydration of the organism. Under what conditions the organism is susceptible of showing fever following dehydration, would be hard to say, but it is very evident that one would expect to find such a state in those infants who had been depleted by severe vomiting.
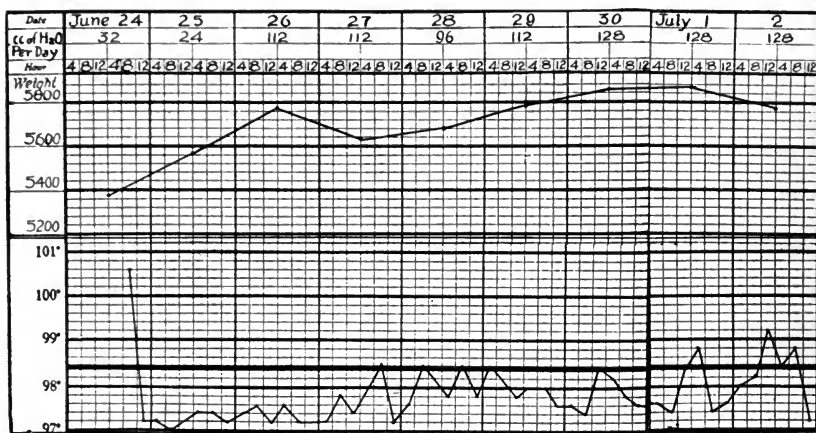
Fig. 14.—Mary Z. Ninth period. Food: Same as in fifth period.

Another practical point is raised as to whether or not the use of thickened food is justified in the treatment of severe vomiting conditions in infancy; such, especially, as pyloric stenosis, pylorospasm and rumination. In the first place, it should be emphasized that the food used in these cases which we have presented was not simply a gruel but was in reality a thick paste. The water content, therefore, was reduced to the minimum, more, in all probability, than would be true in the ordinary thickened feeding used for the type of case mentioned; but even though the temperature did develop, it would have little effect on the general economy of the child, and could easily be reduced by giving some liquid food. A note of warning, however, should be sounded in these cases as to the manner in which the food is changed. If such a temperature has previously existed, the change

from the thickened food to the liquid food should always be made very gradually. We know of at least one child that had pyloric stenosis which died under conditions which in the light of our recent experience could most easily be explained on the basis of an acute collapse following giving liquid food after thickened food was used.

In relation to water content of the body, it would seem that the margin is very narrow between sufficient quantity of water within the body to maintain normal temperature and that present during the febrile period. In other words, after the available water is removed a very slight further reduction will result in the production of temperature. It has been known for some time, and has further been substantiated by Wimberger, that the water available for use by the organism is much more readily obtained from the tissues than from the blood. The question in view of the findings in the last of these cases is raised whether we may regard the water content of the blood as indicative of the state of the organism in relation to the residual water. There was in this instance during the febrile period a very decided reduction in the water content of the blood, as shown by blood counts, hemoglobin estimation and specific gravity. If temperature elevation occurs only when such depletion of the water content of the blood takes place, then we would have a very definite standard by which to judge of the condition in future observations.

CONCLUSIONS

There occurs in infants who have been depleted by vomiting or rumination following the use of a thickened paste feeding, a temperature curve which can most easily be explained on the basis of dehydration, though it is not possible absolutely to rule out absorption of bacteria as a cause, either total or partial, of this temperature. This temperature is unaccompanied by toxic or gastro-intestinal symptoms and there is evidence of a reduction in the water content of the blood during the febrile period.

FEEBLEMINDEDNESS IN HEREDITARY NEURO-SYPHILIS *

OSCAR J. RAEDER

Assistant in Neuropathology, Harvard Medical School; Assistant
Pathologist, Department of Mental Diseases of the
Commonwealth of Massachusetts

BOSTON

The ever persistent effort of nature unassisted to return successive progeny more and more to a normal constitution by combating interceding infections and other adverse influences, is an old and well known fact, especially well known in the course of syphilis. In congenital syphilis this phenomenon has been observed and studied mainly from the somatic viewpoint. The marked improvement in physical condition of each succeeding child born to a syphilitic parent over the preceding one is a matter of every day obstetric experience. From observations on the psyche of congenital syphilitics, and a comparison of mental reactions in children nearer and farther removed from the source of infection, one is convinced that there is a similar progressive degradation of the syphilis toxin affecting the brain cells.

It has been the custom [1] in the neurosyphilis clinic of the Psychopathic Department of the Boston State Hospital and other psychopathic hospitals [2] to apply the Wassermann test to the blood serum of the children of patients found to be afflicted with one or another form of neurosyphilis. Solomon was able to show that 8.4 per cent. of children (in 160 families) returned a positive Wassermann reaction in the blood. Jeans,[3] in a study of 100 syphilitic families, found 78 per cent. of the living children to be syphilitic. The same author [4] reported on 214 seropositive infants and children with hereditary syphilis, and found sixty-six, or 38 per cent., with positive cerebrospinal fluid Wassermann reactions accompanied by gross mental defect in twelve. He also found, in a review of the literature, approximately 33 per cent. of cases with central nervous system involvement, as judged by spinal fluid findings.

An attempt is here made to determine the incidence of central nervous system invasion among this class of children. To this end lumbar punctures were performed and the cerebrospinal fluid subjected

---

* Received for publication September 14, 1920.

1. Solomon and Solomon: The Family of the Neurosyphilitic. Mental Hygiene **2**:71 (Jan.) 1918.

2. Barrett, A. M.: Mchigan State Psychopathic Hospital, Sixth Biennial Report, June 30, 1918, p. 61.

3. Jeans, P. C.: Am. J. Dis. Child. **11**:11 (Jan.) 1916.

4. Jeans, P. C.: Cerebrospinal Involvement in Hereditary Syphilis, Am. J. Dis. Child. **18**:173 (Sept.) 1919.

TABLE 1.— Résumé of Physical and Mental Data of Thirty Children

Case Number	Age, Years	Mental Age, Years	Wassermann Reaction Serum	Wassermann Reaction Cerebro-spinal Fluid	Globulin	Albumin	Cells	Colloidal Gold Test	Remarks
1	13	6 8/12	+	+	0	N	1	5555441000	(Family A)
2	12	8 8/12	—	—	0	N	0	0000000000	Father and mother paretic
3	9	7 4/12	+	—	0	N	1	0012100000	(Table 2)
4	8	4 10/12	+	—	0	N	0	0083310000	
5	4	3 8/12	—	—	0	N	10	0000000000	
6	16	(8.2)	—	:	:	:	:	::::::::::	(Family B) Case 6, Normal
7	12		+	+	0	N	37	5555581000	Father syphilitic, WRS +, CSF —
8	6	3.5	+	—	0	N	1	1111210000	Mother WRS —
9	5	..	—	—	0	N	0	0000000000	(Table 3)
10	11	10 1/5	+	—	0	N	2	0000100000	
11	11	8 11/12	+	—	0	N	1	Negative	Truant; backward at school
12	11 2/12	9 2/12	+	—	0	N	2	Negative	
13	11	2 to 3 (est.)	:	:	:	:	:	......	Imbecile; deaf-mute
14	11 5/12	10 1/2	+	—	0	N	0	Negative	
15	10	Backward in school	+	—	0	N	6	0000100000	(Family C) Father paretic
16	8	..	+	—	0	N	1	0001000000	Mother WRS —, WRFl —
17	6	..	—	:	:	:	:	....	
18	9 1/2	8.1	+	:	0	N	0	Negative	(Family D) Father WRS ; WRFl —
19	4	..	—	:	:	:	:	....	
20	15	..	+	—	0	N	0	Negative	(Family E) Father died of general paresis
21	9.3	11	+	—	0	N	0	Negative	No. 20 has iritis; mother WRS +
22	1 1/2	..	—	:	:	:	:	....	
23	9	8.5	+	+	0	N	3	Negative	Father and mother, WRS +
24	6	..	+	—	2	2	26	5555441100	Hydrocephalus
25	4	..	+	—	0	N	1	Negative	
26	8 9/12	8 2/12	—	:	:	:	:	Negative	(Family F) Mother, WRS +
27	7	..	+	:	0	N	0	1122100000	By test 2% uncooperative
28	6 3/12	4 est.	+	+	+	+	?	....	
29	3 5/12	2 3/5	—	:	:	:	:	....	Saddle nose; high palate; double Babinski
30	2	..	—	:	:	:	:	....	

to the usual analysis. In order to further study the effect of the syphilotoxin on the brain, psychologic tests have been employed. In families in which there are several living children showing variant degrees of syphilitic attrition, it appears that the mental and physical ratings bear a definite relation to each other.

The series of cases studied consisted of thirty children ranging from 2 to 16 years, in either one or both of whose parents there was a positive Wassermann reaction on the blood serum. Most of the parents had neurosyphilis, usually of the paretic type. In some instances, the family became known to the clinic through a congenitally syphilitic child, brought to the hospital on account of mental disease or mental defect (backward and special-class school children). In these families the diseased parent was usually free of syphilitic mental disease though always seropositive.

Results of examinations of blood serum or blood serum and spinal fluid (Wassermann reaction) are given in thirty children either one or both of whose parents were seropositive. Of these children, nineteen showed a definitely positive Wassermann reaction. With few exceptions, the older children, i. e., those born nearest the time of the parental infection, showed a positive Wassermann reaction; the younger and farthest removed usually showed a negative Wassermann reaction. When the infection occurred during a series of pregnancies, those children born before returned a negative Wasserman reaction; those born after, if living, showed marked evidence of hereditary syphilis; succeeding children showed decreasing evidence of it.

On twenty-two of the thirty children a spinal puncture was obtained, and in four of these fluids a positive Wassermann was returned. The colloidal gold test in three of these four positives was typical of paretic neurosyphilis. In the fourth case (No. 28) it was not; there had been some treatment (intravenous arsphenamin), though not enough to cause such a change, even if the fluid might be assumed to have previously been capable of a frank paretic gold curve.

Together with the last mentioned case there were three others (Cases 3, 4, 8) in which a somewhat similar colloidal gold curve was demonstrable. The tubes affected were always the first five, those of the so-called "syphilitic zone," sometimes six and seven, or more, tubes also reacted. This seems to indicate that the colloidal gold reaction in these cases was due to a syphilis toxin or some substance formed by its action, the blood serum already having reacted positively to the Wassermann test and no evidence of other provocative agents forthcoming to claim title to such a gold curve. In all the cases of positive Wassermann reaction in the spinal fluid, the Wassermann reaction was also positive in the blood serum. We have so far encountered no case of hereditary neurosyphilis in which the cerebrospinal

fluid showed a positive, and the blood serum a negative Wassermann reaction. Jeans [4] has reported one such case.

Along with these biochemical reactions, we have been able to show concomitant mental defect. While the psychologic reactions are those of the ordinary feebleminded or backward child, it is doubtful whether or not we can properly use the term mental defect in these cases, although one might be justified in some cases, especially those in which there is a pregenital or fetal aplasia, due to a potent "nascent form," possibly, of syphilotoxin. But in the milder degrees of syphilitic hypophrenia we are certainly not justified in using the term "defect," for with consistent and prolonged treatment, these cases improve, and the intelligence quotient rises correspondingly.

In the relatively older children, those born nearer the parental infection, the physical findings and Wassermann reactions on serum and fluid were not only positive, but they also showed a greater degree of mental deficiency. The children born later, showed less striking biochemical reaction, for although the majority were seropositive by the Wassermann test, their cerebrospinal fluid was usually negative and they showed less mental defect. The third class of children, the youngest born, those farthest removed from the original infection were, for the most part, entirely negative to laboratory tests and showed the least degree of feeblemindedness—but they were backward mentally to some extent.

We observe several psychic terraces ascending pari passu with the demonstrable grades of physical or chemical evidence, and it would seem that the milder forms of mental backwardness in the youngest and healthiest of these children, though syphilis is not demonstrable by laboratory test, is nevertheless due to the syphilis toxin, of too attenuated a form to demonstrate by test tube, but sufficient to register on a more sensitive indicator, the psyche. Furthermore if (as in Case 6) the first child, born before the parent's infection, is normal mentally and physically, and the father and mother are not feebleminded, it seems reasonable to exclude ordinary plasmic feeblemindedness in the younger children born after, but too long after to cause a positive Wassermann. The deduction is that the same cause is operative here as in the older fraternity though the virus may be attenuated. Some careful observers [5] have felt that syphilis is merely incidental to and not genetic of the feeblemindedness.[6] The evidence furnished in family "B" (Table 3) runs counter to this view. Again, in

5. Kuhlmann, F.: Syphilis in Its Relation to Feeblemindedness, J. Lancet **38**:215, 1918.

6. Bevan. L.: Andriezen and Echeverria, quoted by Southard in **Waverly** Researches in Pathology of the F. M., Series 1, p. 43

the study of the pathology of the feebleminded [7] Southard, Fernald and Taft found suspicious evidence of syphilis in the brains of hypophrenics whose serum was negative to the Wassermann test, and in a larger number of cases than is generally suspected. Mott,[8] reporting twenty-two cases of juvenile general paralysis, says most of these patients were mentally deficient from birth.

An attempt has been made to show this graded attenuation of the virus as manifested by psychometric analysis (Fig. 1). All five children (Cases 1, 2, 3, 4, 5, Table 2) of one family are here represented with complete laboratory and psychometric analysis. The consistent rise of the intelligence quotient will be noted in the first three children.

TABLE 2.—SEROLOGY OF FAMILY A (CASES 1, 2, 3, 4, 5 IN TABLE 1)

| | Age, Yrs. | Mental Age, Yrs. | Intelligence Quotient | Wassermann Reaction | | Globulin | Albumin | Cells | Colloidal Gold Test | Remarks |
				Serum	Cerebrospinal Fluid					
Father	..	....	..	+	+	2	2	269	5555443210	Paresis
Mother	..	....	..	+	..	...	..	...	....	Has since developed paresis
Case 1	13	6 5/12	51	+	+	0	Normal	1	5555441000	
Case 2	12	8 8/12	72	—	—	0	Normal	0	0000000000	Feebleminded
Case 3	9	7 4/12	81	+	—	0	Normal	0	0012100000	Feebleminded
Case 4	8	4 10/12	60	+	—	0	Normal	0	0033310000	Feebleminded
Case 5	4	3 8/12	91	—	—	0	Normal	10	0000000000	Backward mentally

TABLE 3.—SEROLOGY OF FAMILY B (CASES 6, 7, 8, 9, TABLE 1)

| | Age, Yrs. | Wassermann Reaction | | Globulin | Albumin | Cells | Colloidal Gold Test | Remarks |
		Serum	Cerebrospinal Fluid					
Father	..	+	—	0	Normal	0	0000000000	No symptoms
Mother	..	—	..	...	....	...	....	Apparently healthy
Case 6	16	—	..	...	....	...	....	Case 6 born in Italy, mentally and physically sound; father contracted lues after emigration
Case 7	12	+	+	0	Normal	37	5555531000	Case 7 born in America; observation case; manic state
Case 8	6	+	—	0	Normal	1	1111210000	Case 8, feebleminded
Case 9	5	—	—	0	Normal	0	0000000000	

The fourth child shows an exceptional variation, dropping below the third child. In the fifth, however, the intelligence quotient rise is again resumed and carried almost to normal.

Just why there is a drop in the fourth case is not evident. Several factors may come into play here. A syphilitic meningitis affecting

7. Fernald, W. E.; Southard, E. E., and Taft, A.: Waverly Researches of the F. M. (Memoirs of Am. Acad. of Arts & Sc.) **4**:117 (May) 1918. (Exudative Lesion Frequent in Stable Institution Series.)

8. Mott, F. W.: Arch. Neurol. **1**:250.

more or less generally the cortical ganglion cells, or some other infectious meningitis, possibly, complicating childhood disease [9] might have augmented the mental defect. In the case of the second child one would have expected a positive Wassermann on the blood serum. This boy [10] was tested but once, whereas the other children's tests were all verified by retest.

Thus in the accompanying figure the curve representing the relative degree of syphilogenic injury to successive children as reflected by psychometric tests in a family in which there is parental syphilis (other adverse influences may react similarly) is shown by the letters a, b, c, d, e, in which the vertical scale represents the intelligence quotient and the base line represents the order of birth. The fourth child drops below in his mental tests and he also (Table 2) shows a

Order of Birth
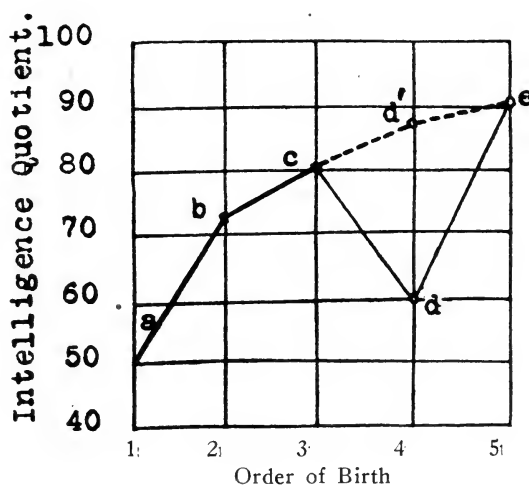
more marked colloidal gold reaction (tests were done the same day with the same reagents). We believe therefore, that this child is an exception, and that otherwise he would have graded somewhere between 80 and 90. The curve would then read as shown by the letters a, b, c, d', e. On the physical side, the progressively decreasing strength of the syphilitic virus is represented by a parallel curve more roughly shown by the blood and spinal fluid analyses;[11] so that this graded attenuation is elicited both pathologically and clinically, the psychical phenomena running abreast the physical reactions in nice correlation.

In the next family (Table 3, Cases 6, 7, 8 and 9), a regular degradation of the syphilotoxin in succeeding members of the fraternity after the infection in the parent is again shown by actual test.

9. Skoog, A. L.: Brain Complications in Measles, J. A. M. A. **74**:1697 (June 19) 1920.
10. Committed to a distant truant school, he was not easily available.
11. See Table 2; also the same curve in Family B, Table 3.

The oldest child was born before the father emigrated to America, where he contracted syphilis. The next child (Case 7) was the first born after the mother and older daughter joined him several years later. This was a girl, in good physical condition, who was brought to the hospital for observation in a manic state. The laboratory tests as shown were all positive for neurosyphilis. The next child in order of birth (Case 8) showed a positive Wassermann reaction in the blood, a negative Wassermann reaction in the fluid, but a trace of suspicious evidence in the syphilitic zone of the colloidal gold test. The next child in order (Case 9) gave entirely negative reactions, both on the blood serum and spinal fluid. The physical attenuation curve is here regularly drawn both as to Wassermann reaction and the colloidal gold test.

The correlations of mental age with physical tests are unsatisfactory or impossible here because psychometric figures are incomplete (Case 9) and the unreliability of the mental age in Case 7 (manic state with rapid-fire associations).

SUMMARY

Blood and spinal fluid examinations have been made on twenty-two children, born of syphilitic parentage. It has been found that various degrees of syphilitic infection are present in a definite order in a family of several children, the oldest, born soonest after the parental infection, showing the greatest injury and the succeeding children showing milder degrees in order.

Psychometric examinations done on these children show corresponding psychic terracing going pari passu with the grades of physical defect.

The youngest children of a family though seronegative, have been found to be feebleminded to a slight degree. The syphilitic injury to the nervous system either projects beyond the physical defect or by reason of the peculiar reactions of the brain compared with other organs we have a finer indicator in it than in ordinary tissues. Or, again, while the central nervous system may recover more rapidly in succeeding births as registered by the Wassermann, colloidal gold and other tests, the recovery may not be as complete.

CONCLUSIONS

Mental deficiency in congenitally syphilitic children of not feebleminded parents is in the majority of cases due to syphilis.

The virulence of the congenital syphilis toxin in a given fraternity as evidenced by psychometric analysis and biochemical test varies inversely with the order of birth.

THE ELECTROCARDIOGRAM IN NORMAL CHILDREN *

MAX SEHAM, M.D.
MINNEAPOLIS

Electrocardiography is that phase of cardiography which deals with the direction, the time relations and the magnitude of the "action currents" of the heart.[1] It does not register the strength of the contraction of the heart muscle, but it is merely the expression of the electrochemical processes concerned with the contraction of the heart muscle.

Electrocardiography in children is a large and fertile field for clinical research. In spite of the many and noteworthy contributions that have been made to the diseases of circulation in general with the aid of the electrocardiograph, no attempt has as yet been made in this country at a systematized and comprehensive investigation of this subject in children. In the electrocardiograph there are great possibilities for a study of physiologic peculiarities of the normal heart of the child. Through it we can obtain a clearer conception of the peculiarities of the heart mechanism during the different periods of growth. The preciseness of this method will allow us to correlate more accurately certain clinical symptoms with their associated arrhythmias and other forms of impulse disturbances. Since the electrocardiogram is an expression of the muscle rather than of the valves of the heart, we may obtain data, otherwise unobtainable, about the heart muscle, and we may hope to further our knowledge of the prognosis of heart disease, about which we know practically nothing.

This paper is the first of a series on this subject. It includes (1) the study of the form of the curves; (2) the heights of all deflections; (3) the rate; (4) the rhythm; (5) the transmission time, and (6) the relation between the right and left ventricles of the heart during the period of childhood. Electrocardiograms of 101 children (including prematures), from one hour to 13 years of age, are recorded. They were all normal as far as clinical examinations could determine.

The first investigation of the electrocardiogram in the child was undertaken in 1908 by Funaro under the direction of Nicolai.[2] He

1. Lewis, T.: Electrocardiography and Its Importance in the Clinical examination of Heart Affections, Brit. M. J. **1**:45, 1912; **2**:1421; 1479, 1912.

2. Funaro and Nicolai: Electrocardiogram of Nurslings, Zentralbl. f. Physiol. **58**: 1908.

studied forty-five children, most of whom were infants. He was the first one to describe the deep S in Lead I in nurslings. This has since been corroborated by other observers. His work is open to criticism in that he employed only the first lead, and he does not state whether his subjects are normal or abnormal.
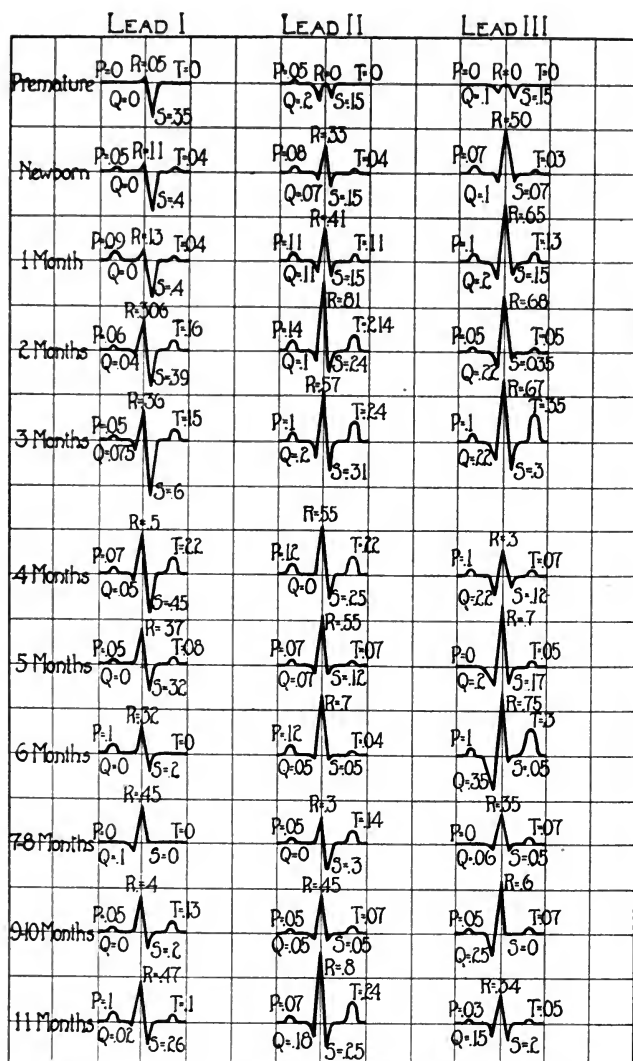
Fig. 1 a

Fig. 1. — Composite electrocardiograms of normal children of all ages. Exact heights of all deflections in millivolts. Each square represents 5 scale divisions of 0.5 mvlt.
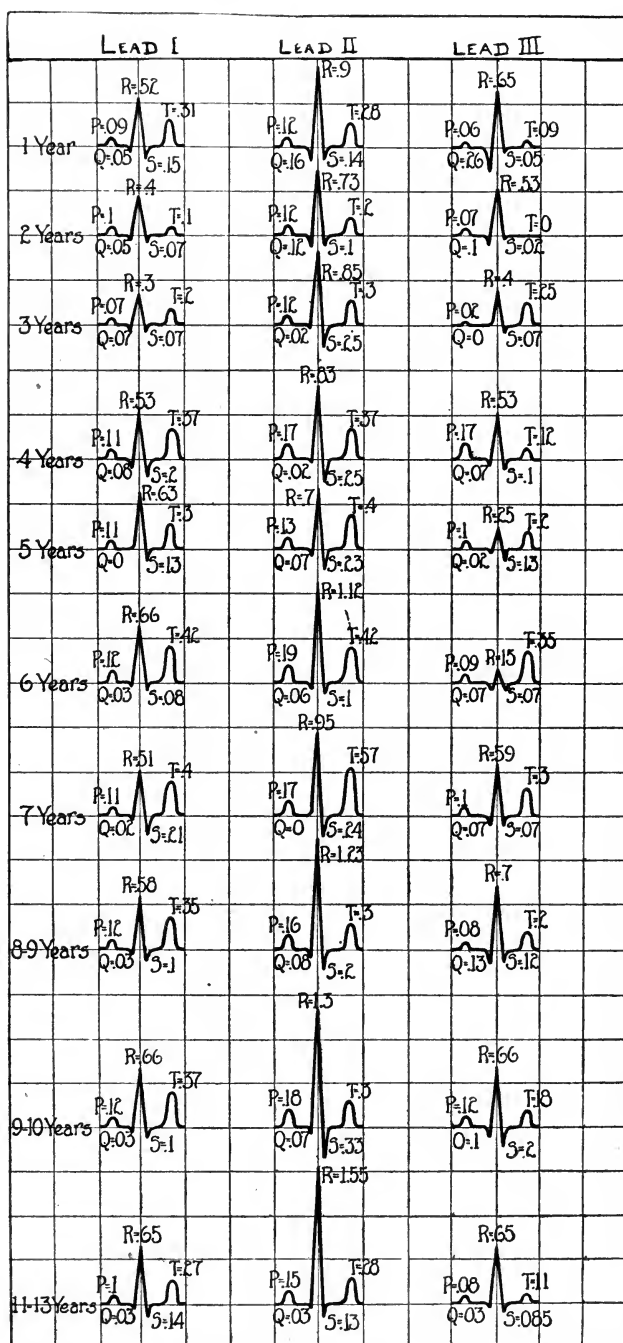
Fig. 1 b

A little later in the same year, Heubner [3] made a similar study. He also took tracings of the first derivation only. He either waited for his subjects to fall asleep or he administered chloral hydrate to keep them quiet. He also noted the deep S and the very small or absent R in new-borns. He thought that the change from the infantile type of electrocardiogram to that of the adult occurred at about the eleventh or twelfth month. Hecht,[4] in 1912, contributed the first comprehensive treatise on this entire subject. Although in this work he made a complete study of the physiologic peculiarities of the heart of the child, he did not establish a composite curve that could be used as a guide for the normal at all ages of childhood.

Krumbhaar and Jenks,[5] in 1916, made a study of forty-five normal children of all ages, from which they have derived their composite electrocardiograms. With the exception of the work of Hecht (1912) and Krumbhaar (1916), there has been no attempt to investigate the peculiarities of each of the deflections of the normal electrocardiogram of the different periods of childhood.

<center>TECHNIC AND PROCEDURE</center>

It is much more difficult to employ the electrocardiograph in children than in adults. For this reason it is especially important to mention some of the obstacles one meets in working with children. The subject is connected by means of copper electrodes to the switchboard. The right arm, left arm and left leg are used. I used for the new-born small, tightly fitting copper cuffs held together by rubber bands. For the older children the electrodes used for the adult are suitable.

Absolute quiet is the most important factor in securing accurate tracings. In the new-born it is better to take the tracings while the baby is asleep. A nipple in the mouth for a few minutes before the experiment will keep the baby quiet long enough to take a satisfactory record. In working with infants, it is very hard to keep the string out of the field, and it is especially important to keep the string neither too tight nor too loose. The slightest movement due to coughing, sneezing or crying will cause marked deflection of the string. Such a tracing must be discarded. In young nurslings the attention can be held by a lighted match or a bright object of some kind.

It is also important to wash carefully with soap and water the

3. Heubner: Elektrokardiography des Säuglings und des Kindes, Monatschr. f. Kinderh. **7**:66, 1908.

4. Hecht, A.: Der Mechanisms der Herzaktion im Kindesalter, Ergebn. d. inn. Med. u. Kinderh. **11**:324, 1913.

5. Krumbhar, E. B.: Electrocardiographic Studies in Normal Infants, Heart, **6**: 1915.

parts which come in contact with the electrodes, for the oil in the skin increases the resistance to the current. There seems to be about as much skin current generated by children as by adults, and this must be exactly compensated by throwing an equivalent amount of current into the circuit in the opposite direction.

The position of the electrodes must be watched carefully, especially in nurslings. The slightest wriggling will loosen the electrodes and cause either low deflections or none at all. They must be held firmly, preferably by means of rubber bands. The bare legs or arms must be kept from touching each other so that there will be no crossing of the current.

All of the records were obtained either at the heart station at Millard Hall at the University of Minnesota or at the University Hospital 400 feet away from the electrocardiograph. When the work was first undertaken, at least two tracings were taken at each sitting, and in some instances three or even more. It was found that although the height of the deflections differed slightly in the same subject, the form was quite constant. It was not necessary to administer any drugs (as was done by some of the above mentioned investigators) in order to obtain satisfactory records. All three leads were taken for each child. Only those who were within the normal limits of weight and height, with normal shaped chests, and hearts that showed no abnormal signs were selected. In this study the same technic was used with all children. The child lay on the back, the room was perfectly quiet, and the time was usually between 9 and 11 a. m., after the first feeding. The same electrodes were always used. The pads for the electrodes were boiled after being washed in soap and water, and before being applied were immersed in saline solution. The string was so adjusted that one millivolt of current caused a deflection of one centimeter. Platinum strings were used of about 3,500 ohms resistance and 0.02 second deflection time. The accompanying tables are calculated on the basis of one millivolt—one centimeter. The body resistance does not vary appreciably in new-borns and older children.

P Wave.—It is the consensus of opinion among all authorities that the P wave represents auricular activity. Although there are exceptions to the rule, the height of P may be considered as representative of the summation of action currents in the auricles, while the distance from the beginning of P to the beginning of R (the so-called P-R interval) is representative of the period of impulse conduction through the auricles and through the conducting tissues to the ventricles.

Hecht [4] has attempted to establish a normal P for childhood, by dividing the height of R by the height of P of the same lead, thereby

getting what he calls the auricular quotient. He found that in new-borns the quotient was 68 per cent., and in older children (taking the average of all children aged from 2 to 13 years) 12.5 per cent. I do not believe that this can be used as a reliable guide for the height of the P. In the first place, he used only derivation I, whereas throughout childhood P in Leads II and III is higher than in Lead I; secondly, in order to have an accurate guide for all ages, it would be necessary to divide childhood into four periods at least, instead of two, as is done by Hecht; thirdly, in very young infants, especially in the new-born, the R in Lead I is small and that would decrease the quotient for the entire four periods of childhood. Linetzky, in working with adults only, found that P did not vary with age. His averages for the height of P from 20 to 50 years were from 1.2 to 1.3 mm.

In my investigations I found the following: (Fig. 2).
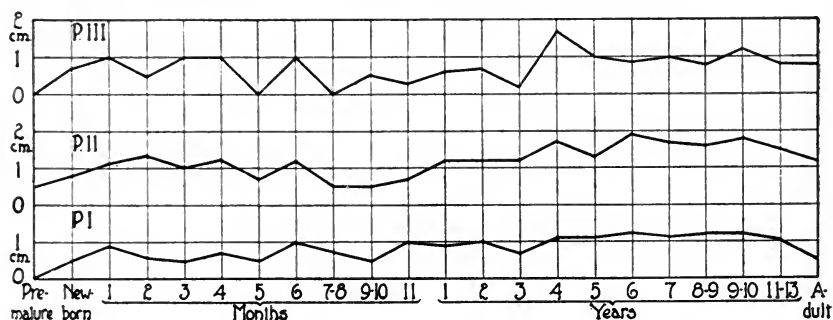
Fig. 2.—Height of P deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

In the two prematures none of the three leads showed the auricular deflection. From birth through the entire period of childhood P is constant and definite. In only two of the entire series was P absent. In general, the P is higher in childhood than in the adult. In derivation one, the average height during the first two years is 0.6 mm. (+) and from 2 to 13 years it is 1.0 mm., whereas in the adult it is 0.5 mm. In this lead during the first few months of life, P is higher than in the adult, although it is not quite so broad. In Lead II, the average for the period of infancy is 1.2 mm. and for the latter part of childhood it is 1.5 mm. In this derivation, the P is also higher throughout childhood than in later life. Beginning with a height of 0.5 of a scale division [6] at birth, it abruptly increases during the first few months to slightly over one scale division. During the rest of childhood it remains between 1 and 2 mm. as compared to an average of 1.2 mm. in the adult. The height of this deflection in this lead is

---

6. (+) 1 mm. = 0.1 m volt = 1 scale division.

less constant than in the other two leads. Of the entire series, I found either a diphasis or an inverted P wave in eight records; six of these were in new-borns, one in a child 3½ years old, the other in that of one six years old. In two cases P_1 and P_3 were inverted. Four of these latter were diphasic and one was very broad, being almost flat at the top.

The clinical significance of an electronegative P has not been definitely established. Carter in an investigatiion of the inverted P in derivation three concluded that it was caused by (1) an ectopic rhythm as the result of a definite change in the location of the pacemaker, and by (2) disturbances in the respiratory rhythm. He found that, especially in Lead III, P was very much influenced by the different phases of respiration; that the P was lower at the end of respiration than at the beginning; and that the slight rotation of the heart about the sagittal axis of the body, which may be brought about by a very deep
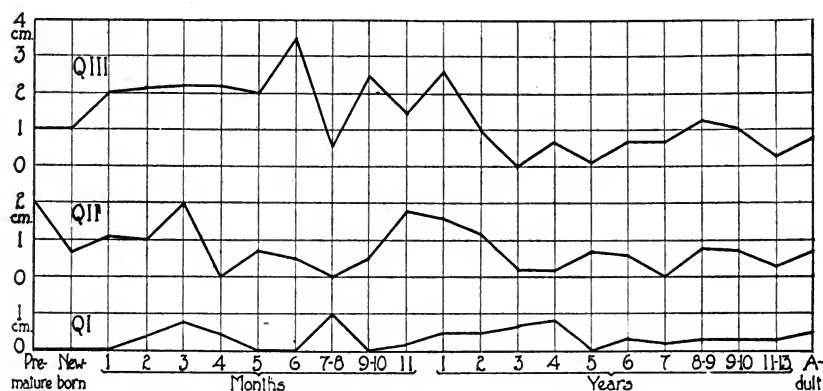
Fig. 3.—Height of Q deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

inspiration causing a change in the position of the heart, also changed the height and shape of the P.

Goddard[7] noted the great frequency of an inverted P_6. In 700 cases P_1 was inverted in four, P_2 in seven, and P_3 in seventy-five.

DISCUSSION

If we can assume that there is any direct relation between the size of the P and the structure of the auricle, then we can readily explain the relatively high P during the first year of life by our anatomic data. We know that the foramen ovale in a large number of instances continues to remain open until the end of the first year. This may

7. Goddard: Changes in the P wave of the Human Electrocardiogram. Arch. Int. Med. **16**:632 (Oct.) 1915.

increase the work of the auricles during that time. Gundobin [8] states that the auricles during the first year are from 21 to 22 per cent. of the weight of the ventricles as compared to 20, 18 and 17 per cent. in the following years.

There is no greater frequency of abnormal P-waves in this series than in those reported on normal adult hearts.

Q Wave.—There has been and still is a difference of opinion as to the physiologic significance of the Q deflection. Q is a downward deflection at the beginning of the ventricular complex. It is not always present. It is important in the electrocardiogram of childhood. Hoffmann,[9] who seems to have the most commonly accepted explanation for the Q deflection, believes that it represents the beginning of the ventricular impulse conduction. According to Lewis,[10] the Q in Lead I represents the spread of left ventricular activity, and in Leads II and III he believes it to be a right ventricular event.

Krumbhaar [5] noted the relatively deep Q in childhood, especially in Leads II and III. The average of the Q in these leads is less than 1 mm. in the adult; whereas in the infants he examined he found the Q relatively and absolutely deeper.

In my series I found also, that, in general, the Q of Leads II and III was deeper than in the adult (Fig. 3). In Lead I, up to the first month, Q is absent; from the first to the fifth month, the Q is variable and indefinite, never reaching deeper than 0.7 mm. From the eleventh month on, there is a gradual increase of Q which averages about the same as in the adult. From the fifth year there is a remarkable constancy which persists throughout the rest of childhood, averaging about 0.4 of a scale division. This fact, namely, that during the first year the Q_1 is relatively of diminished depth and in the majority of instances is absent, and that after the first year and during the rest of childhood Q_2 and Q_3 become larger, the average being equal to that of the adult, corroborates the theory of Lewis that Q_1 represents left ventricular activity. Q_2 is not quite so uniform in its depth. During the first three months it is rather deep, running on an average of one scale division. From the fourth to the ninth month, it remains more uniformly at the level of one-half of a scale division, and from the ninth month to the second year it increases to two mms. From the third year on, it averages 0.5 mm. which is slightly less than in the adult. Q_3 is deeper during the first period of life than Q in

8. Gundobin: Die Besonderheiten des Kindesalters, Berlin, 1912.

9. Hoffmann, A.: Die Arythmie des Herzens im Elektrokardiogramm, München. med. Wchnschr. **44**:1909; Herz und Konstitution, Jahreskurse fuer aertzl. Fortschr., February, 1918.

10. Lewis, T.: Observations on Ventricular Hypertrophy, Heart **5**:367, 1914.
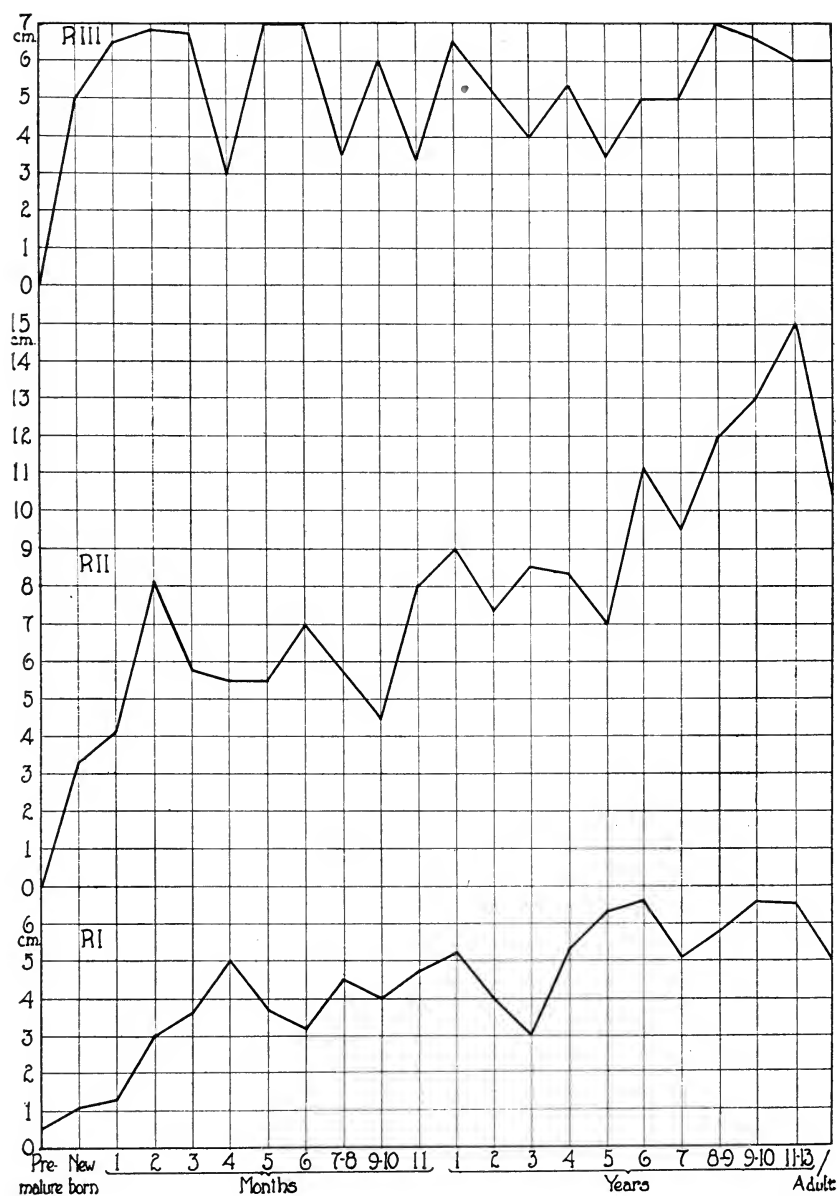
Fig. 4.—Height of R deflection. Each square represents 0.5 mvlt. or 5 scale divisions.

the other two leads. From the fifth month to the second year, it is somewhat variable. At the second year, there is a sudden diminution and the figure remains low throughout the rest of childhood. The average for the first two years is 0.9 of a scale division. From the age of 2 on it is 0.6.

DISCUSSION

If the theory of Lewis is correct, that Q_1 represents left ventricular activity and Q_3 right ventricular activity, then the depths of this deflection in the third derivation, as shown in Figure 3, give corroborating evidence of right ventricular preponderance in nurslings.

R Wave.—The R wave is the most constant and important electropositive deflection of the ventricular complex. There is still, however, some difference of opinion as to the physiologic significance of this wave. Hoffman [11] is of the opinion that the R wave represents the impulse conduction through the ventricular fibers or the excitation of the muscle which immediately precedes the actual contraction.

Linetsky [12] found that in adults the R becomes higher with age and with the increase of the heart size. He found the average height in a series of 300 adults to be from 11 to 14 mm. (Lead II). In my study, I found that in childhood (Fig. 4) the R generally becomes much higher than it is in the adult, although in Lead I the R is lower in the premature and in the new-born than in any other period of life. From the first month there is an abrupt ascent which reaches its peak in the fourth month. From then on, the averages form an up and down curve until the fourth year. During the second and third year, I have used the averages of only two cases. This may account for the unexpected drop of the R wave after there had been an ascent (Fig. 4). After the fourth year, the high R is suggestive of a change to a left ventricular preponderance.

R in Lead II shows a very definite ascent which is consistent with the anatomical change in the mass relationship between the right and left ventricle. No R_2 was found in the premature, but immediately after birth the R_2 rises very rapidly. From the first to the fourth year the curve is about the same. From the fourth year on, there is another increase which passes the adult height at six years. From then to the end of childhood it becomes higher and higher, so that at puberty it averages 15 mm. as compared to 10.3 mm. in the adult.

11. Hoffmann, A.: Demonstrationen zur Lehre von der Form des Elektrokardiogramms, Verhandl. d. deutsch. Kong. f. innere Med. **18**:429, 1911.

12. Linetzky. Die Beziehungen der Form des Elektrokardiogramms zu dem Lebensalter, der Herzgroesse und dem Bludrucke, Ztschr. f. exper. Path. u. Therap. **9**:669, 1911.

R_3 is variable throughout the entire period of childhood. It is absent in the premature, but during the first month of life it reaches a rather high measurement which it retains until the fourth month. For some unknown reason it falls and stays at a low level until the eighth month. From then on, until the fourth year, it is again variable. After that it increases and remains high throughout the rest of childhood. For the first two years it averages 5.5 mm.; from then until 13 years it averages 5 mm.

S Wave.—The S is still a subject of dispute. It is not always found in the normal electrocardiogram. In Lead I, S is a right ventricular event, and in Lead III it is a left ventricular event. So far
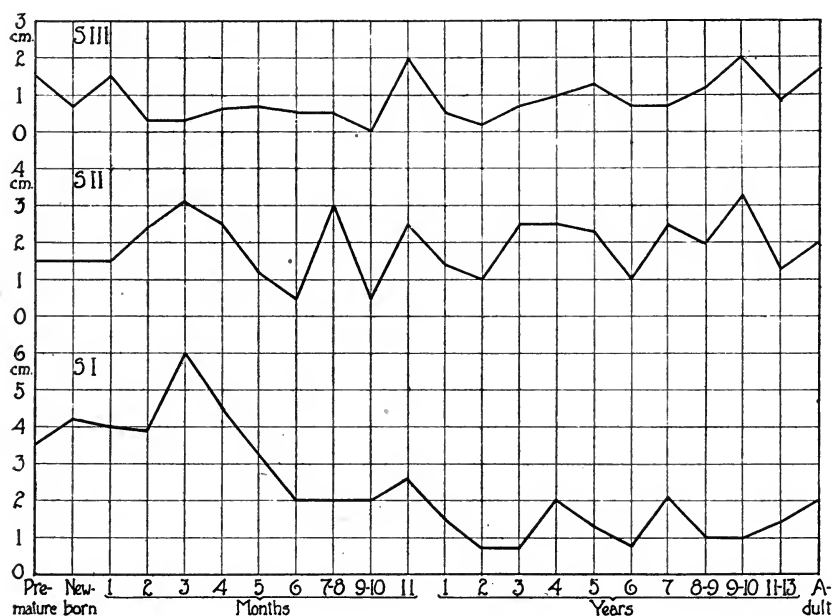
Fig. 5.—Height of S deflection. Each square represents 0.5 mlvt. or 5 scale divisions.

back as 1908 Funaro,[2] working with Nicolai, found a deep S in a large majority of the forty-five infants examined. Nicolai concluded that this was due either to a left ventricular hypertrophy or to a more horizontal position of the heart at this age.

At almost the same time Heubner[3] also found this same characteristic deep S_1. There is no difference of opinion regarding the fact that S_1 is deep during the first few months of life. There is some difference, however, as to when the S disappears. Some believe it disappears as early as the third month, others at about the seventh or eighth month; others, again, are not sure of a permanent change

until the end of the first year. There are also differences of opinion among the earlier observers as to the explanation for this characteristic curve. Is it due to the higher and more horizontal position of the heart on account of the high diaphragm? Or, is it due to the fact that in this period the right ventricle is relatively preponderant over the left? I have been able to confirm the opinion of Grau [13] and others that change of position does not have any influence on the shape of the S wave. On the other hand, using the formula of White [14] ($U_1 + D_3$) — ($D_1 + U_3$) = constant, to determine the ventricular preponderance and comparing the electrocardiograms of the period of infancy month by month with the size and thickness of the ventricles of the same ages, one is justified in concluding that in the anatomic relationship between the right and left ventricles lies the explanation of the deep S in Lead I.

In my series, S_1 is both relatively and absolutely greatest during the first three months of life (Fig. 5). From its peak at the end of the third month it diminishes abruptly to the sixth month. Then holding a level until the tenth month, it has another diminution until it reaches its minimum deflection at about the beginning of the second year. From then on it increases slightly and remains about the same throughout the rest of childhood. In the latter part of childhood it is slightly deeper than in the adult.

Lead II is generally lower during the period of infancy than in later childhood, although the differences between the periods is much less than in Lead I. The average from three years on is about one scale division higher than during the period of infancy.

Lead III shows a curve somewhat similar in its inconstancy to Lead II. The average of S_3 for the entire childhood is lower than that of S_2. From birth to the third year the curve is too variable to draw conclusions from; but from the third year on, the curve is more constant and averages less than that of the adult.

The influence of crying, respiration and position on the shape and size of S have all been studied. The occurrence of a deep S_1 in older children will be discussed in another paper in connection with atypical electrocardiograms in normal children.

T Wave.—The T wave is the last of the ventricular complex. There is still a difference of opinion as to its meaning.

---

13. Grau, H.: Ueber den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Ztschr. f. klin. Med. **69**:281, 1909; Zentralbl. f. Physiol. **23**:440, 1910.

14. White, P.. and Block, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, Am. J. M. Sc. **156**:17, 1918.

Linetzsky believes that in the adult the T wave decreases with the increase of age, especially in the very old. He found that at about 45 years of age it was quite constant, averaging 3 mm. From then on, it decreased to 2.1 mm. The decrease of the S was in direct proportion to the increase of the R wave. Krumbhaar in his work with children found no T in the first week of life, but he found it constantly after the third week highest in Lead II and lowest and frequently inverted in Lead III. Hecht found it present, although not uniformly, in the new-born.
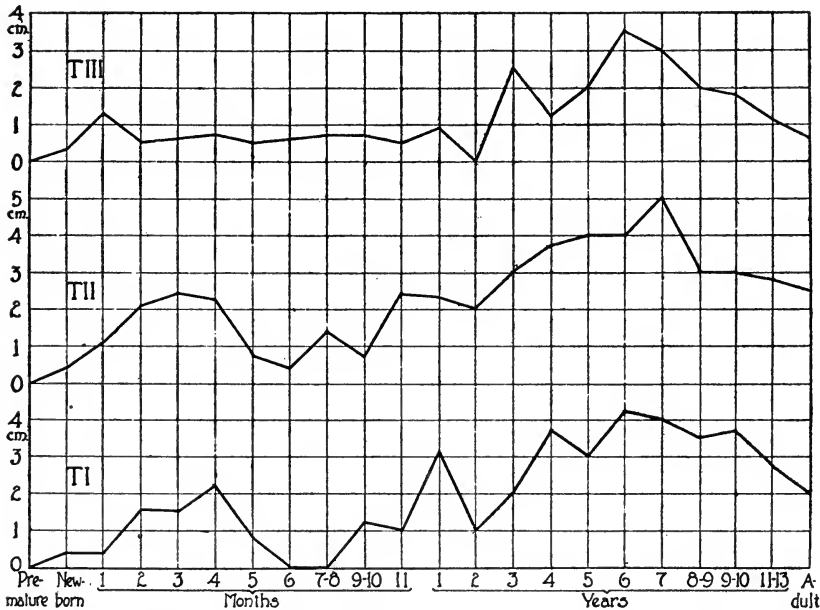
Fig. 6.—Height of T deflection. Each square represents 0.5 mlvt. or 5 scale divisions.

In the child the T is the phase of the ventricular complex most susceptible to unexplained changes. In my series of twenty-two cases I found no T in the premature, but right after birth, for the first ten days, it was present in 39 per cent. of the cases in Lead 1, 77 per cent. in Lead II, and 47 per cent. in Lead III (Fig. 6). After the first month it was quite constant. T_1 is more regular in its developmental changes than in the other two leads.

In Lead I, from the first to the fourth month, there is a sudden increase; then a sudden drop to the seventh month, and again an increase to the second year. I can see no physiologic explanation for such a change. From the second year on there is again an increase which after the fourth year remains about the same. In this lead

TABLE 1.—Twenty-Two Normal Electrocardiograms of Infants Aged from 1 Hour to 11 Days

No.	Age	Weight, Gm.	Sex	P 1	P 2	P 3	Q 1	Q 2	Q 3	R 1	R 2	R 3	S 1	S 2	S 3	T 1	T 2	T 3	Rate
1	Premature 7 mo. 3 du.	2,110	M	0	0.1	0	0	0.3	0.2	0.1	0	0	0.4	0.2	0.1	0	0	0	170
2	Premature 8 mo. 1 wk.	2,310	M	0	0	0	0	0.1	0	0	0	0	0.3	0.1	0.2	0	0	0	180
3	4 hours	3,115	M	0	0	0	?	0.02	0.25	0.3	0.32	0.15	0.3	0	0	?	0	0	110
4	8 hours	3,440	M	0.09	0.1	0.1	0	0.15	0.1	0.15	0.5	0.8	0.5	0.15	0.09	0	0	0	108
5	16 hours	2,840	M	0.1	0.15	0.05	0	0	0.05	0	0.3	0.45	0.25	0.2	0.2	0.18	0.02	0	152
6	18 hours	2,440	M	0.10	0.05	0	0	0.1	0.05	0.05	0.3	0.3	0.3	0.1	0	0	0	0	160
7	24 hours	3,600	M	0.05	0.15	0.05	0	0.01	0	0	0.22	0.35	0.22	0.15	0	0	0	0	102
8	2 days	3,230	F	0.1	0	0	0	0.05	0.1	0.2	0.3	0.75	0.3	0.2	0	0	0	0.06	135
9	2 days	3,125	M	0	0	0	0	0.1	0	0.1	0.25	0.3	0.3	0.15	0.05	0	0	0.09	
10	2 days	2,940	F	0.05	0	0.05	0	0	0	?	0.05	0.09	0.3	0	0.1	0	0	0	128
11	3 days	3,625	F	0	0.1	0.08	0	0	0.1	0.1	0.1	0.09	0.4	0.09	0.1	0.05	0.1	0.1*	128
12	3 days	3,095	M	0.05	0.1	0.1	?	0	0.2	0.1	0.4	0.4	0.6	0.15	0.2	0.2	0.05	?	
13	3 days	3,250	F	0.1	?	0.1	*	?	0	0.3	*	0.9	0.7	?	0.2	0.1	?	0.09	132
14	4 days	3,850	M	0.1	0.15	0.1	0	0.1	0.1	0.2	0.4	1.0	0.7	*	0	0.1	0.1	0.09	130
15	4 days	3,100	M	0.15	0.1	0	0	0.1	0.1	0.1	0.4	0.5	0.5	0.2	0.05	0.1	0.1	0	140
16	5 days	2,800	F	0	0.05	0	0	0.05	0.05	0.5	0.3	0.2	0.4	0.3	0.2	0.05	0	0	174
17	5 days	2,790	M	0.1	?	0.1	0	?	0.2	0.05	0.1	0.1	0.3	0.1	0	0.2	?	0.08	135
18	5 days	3,420	M	0.05	0.1	0.08	0	0.05	0.15	0.3	?	0.9	0.7	?	0.2	0.05	0.09	?	202
19	6 days	2,720	F	0	?	?	0	?	?	0.1	?	0.3	0.5	0.05	0.05	0	0.09	?	172
20	6 days	3,440	F	0	?	0.05	0	?	0.1	0	?	?	0.2	?	0.2	0	?	?	160
21	9 days	4,000	F	0	0.15	0.06	0	0.1	0.1	0.1	0.5	0.4	0.3	0.3	0.2	0	0.1	0.09	160
22	9 days	4,000	F	0	0.2	0.25	0	0.15	0.3	0	0.5	0.7	0.5	0.3	0	0	0.1	0.5	180

One scale division represents 1 mm. in actual height and 0.1 mvlt. in potential.
* indicates inverted.

TABLE 2.—FORTY-FIVE NORMAL ELECTROCARDIOGRAMS OF INFANTS AGED FROM 11 DAYS TO 1 YEAR

No.	Age	Weight, Gm.	Sex	P 1	P 2	P 3	Q 1	Q 2	Q 3	R 1	R 2	R 3	S 1	S 2	S 3	T 1	T 2	T 3	Rate
1	11 days	2,815	F	0	0.05	0.1	0	0.05	0.1	0.05	0.04	0.5	0.4	0	0.05	0	0.1	0.2	148
2	13 days	3,200	F	0.1	0.09	0.1	0	0.1	0.2	0.1	0.5	0.6	0.5	0.2	0.3	0	0.1	0.1	138
3	18 days	2,440	M	0.1	0.05	0	0	0.1	0.05	0.05	0.5	0.3	0.3	0.1	0	0	0	0	160
4	24 days	3,360	M	0.1	0	0.1	0	0	0.2	0.15	0.15	0.2	0.6	0.15	0.1	0.1	0.05	0.09	132
5	3 wks.	3,800	M	0.1	0.15	0.1	0	0.1	0.3	0.15	0.8	0.6	0.4	0.3	0.1	0.05	0.2	0.1	124
6	3 wks.	3,600	M	0.1	0.1	0	0	0.2	0.1	0.1	0.4	0.9	0.3	0.1	0.2	1.5	0.1	0.1	128
7	5 wks.	4,115	F	0.05	0.1	0.1	0.15	0.3	0.3	0.3	0.9	1.2	0.7	0.5	0.6	1.5	0.4	0.3	**136**
8	5 wks.	4,030	M	0.15	0.2	0	0	0.3	0.1	0.1	0.6	0.8	0.4	0.3	0.1	0.1	0.1	0.1	128
9	6 wks.	3,840	F	0.1	0.15	0.1	0	0.3	0.4	0.5	0.6	0.9	0.6	0.4	0.1	0.2	0.2	0.2*	110
10	6 wks.	3,900	F	0	0.1	0.1	0	0.25	0.3	0.3	1.0	1.0	0.6	0.3	0.15	0.05	0.05	0	147
11	6 wks.	3,143	F	0.1	0.15	0.05	0	0.1	0.15	0.15	0.6	0.8	0.4	0.1	0	0.15	0.1	0.1	165
12	6 wks.	3,820	F	0.1	0.15	0.09	0	0.05	0.1	0.35	0.4	0.4	0.6	0.25	0	0.05	0.1	0.1	140
13	6 wks.	3,720	F	0.05	0.1	?	0.05	0	?	0.3	0.3	?	0.4	0.1	?	0.1	0.05	?	
14	6 wks.	3,915	F	0.05	0.1	0	0.05	0.15	0.2	0.15	0.6	0.6	0.35	0.1	0.1	0.1	0.15	0	
15	2 mos.	4,300	M	0.1	0.1	0	0.05	0.1	0.4	0.3	0.8	1.0	0.3	0.2	0.1	0.1	0.4	0	160
16	2 mos.	4,500	M	0.1	0.09	0.1	0.1	0.2	0.2	0.2	0.1	0.4	0.4	0.25	0.3	0	0	0	
17	2 mos.	4,560	M	0.05	0.1	0.05	0	0.05	0.15	0.5	0.55	0.3	0.8	0.25	0.05	0.1	0.2	0.1	180
18	7 wks.	4,320	M	0.05	0.2	0	0	0.1	0.1	0.2	0.3	0.1	0.35	0.2	0.05	0.2	0.1	0.1	150
19	7 wks.	4,020	M	0	0	0.1	0.1	0.3	0.4	0.4	0.25	0.3	0.5	0.8	0.3	1.5	0.2	0.2	
20	10 wks.	4,940	F	0.1	0.2	0.1	0.2	0.3	0.3	0.3	0.6	0.7	0.5	0.3	0.8	0.3	0.3	0.6	148
21	12 wks.	6,110	M	0	0.2	0.2	0	0.2	0.2	0.6	0.6	1.5	0.8	0.3	0.1	0.3	0.3	0.5	138
22	3 mos.	5,840	F	0.1	0.05	0.09	0	0	0.15	0.3	0.3	0.2	0.4	0.2	0.15	0.15	0.05	0.05	120
23	3½ mos.	6,120	M	0.1	0.2	0.15	0	0	0.3	0.6	0.8	0.4	0.5	0.3	0.1	0.2	0.4	0.1	117
24	4 mos.	6,580	M	0.05	0.05	0.05	0	0	0.15	0.3	0.2	0.2	0.4	0.2	0.15	0.15	0.05	0.05	150
25	4 mos.	6,850	M	0.09	0.1	0.1	0.1	0.05	0.05	0.6	0.2	0.2	0.4	0.1	0.5	0.15	0.1	0.1	130
26	5 mos.	7,100	M																150

(Weights below in Lbs.)

No.	Age	Weight, Lbs.	Sex	P 1	P 2	P 3	Q 1	Q 2	Q 3	R 1	R 2	R 3	S 1	S 2	S 3	T 1	T 2	T 3	Rate
27	5 mos.	15	M	0.05	0.05	0	0	0.1	0.09	0.5	0.5	0.2	0.4	0	0	0.1	0	0.12	135
28	5½ mos.	14	M	0.1	0.05	0	0	0.1	0.25	0.3	0.65	0.7	0.25	0.2	0.15	0	0	0	125
29	6 mos.	14	M	0.1	0.2	0.1	0	0.1	0	0.45	1.15	1.1	0.2	0.1	0.1	?	0.4	0.3	135
30	6 mos.	5,320 Gm.	M	0.1	0.05	0	0.1	0	0.08	0.2	0.3	0.4	0.2	0.1	0.1	0	0.05	0.1	
31	8 mos.	15	F	0	0.05	0.01	0.1	0	0	0.4	0.3	0.3	0	0.3	0.1	0	0.2	0.1	
32	8 mos.	18	M	0.05	0.05	0.05	0	0	0.1	0.5	0.5	0.4	0.1	0.3	0	0.05	0.15	0.05	135
33	10 mos.	20	F	0.05	0.05	0.05	0	0	0.05	0.2	0.5	0.3	0	0.06	0.2	0.2	0.1	0.05	110
34	11 mos.	19	F	0.09	0.1	0.09	0.1	0.1	0.15	0.6	0.7	0.3	0.15	0.3	0.25	0.15	0.3	0.09	180
35	11 mos.	17	F	0.1	0.1	0	0.1	0.1	0.15	0.3	0.6	0.7	0.35	0.3	0.2	0.2	0.1	0.09	110.5
36	11 mos.	17	F	0.15	0	0	0.1	0.25	0.1	0.55	0.8	0.25	0.2	0.3	0	0.15	0.25	0.1	120
37	13 mos.	19	F	0.05	0.2	0.15	0.1	0	0.1	0.4	0.1	0	0.2	0.3	0.1	0.2	0.25	0.1	135
38	14 mos.	21	M	0.1	0.1	0.05	0.15	0.4	0.5	0.8	0.7	0.4	0.2	0.25	0	0.15	0.25	0.2	140
39	14 mos.	18	F	0.1	0.2	0	0.05	0.3	0.4	1.1	1.2	1.0	0.2	0.1	0.1	0.3	0.5	0.2	105
40	15 mos.	22	M	0.1	0.1	0.05	0.1	0	0.2	1.1	1.7	1.0	0.1	0.35	0.15	0.6	0.2	0.2	105
41	16 mos.	22	M	0	0	0.1	0	0.2	0.2	0.35	0.4	0.8	0.2	0.05	0	0.3	0.1	0	135
42	16 mos.	24	M	0.05	0.1	0.05	0.1	0.1	0.2	0.45	0.9	0.7	0.2	0	0.15	0.2	0.15	0.1	145
43	19 mos.	27	M	0.1	0.1	0	0.1	0.2	0.2	1.0	0.7	0.4	0.2	0.1	0	0.2	0.3	0	110
44	19 mos.	29	F	0.2	0.1	0.1	0.1	0.2	0.2	0.5	1.0	0.6	0.2	0.3	0.1	0.3	0.3	0.2	115
45	1 year	20	M	0	0.1	0	0	0	0.1	0.5	1.0	0.55	0	0	0	0.2	0.25	0	

TABLE 3.—TEN NORMAL ELECTROCARDIOGRAMS OF CHILDREN AGED FROM 2 YEARS TO 5 YEARS INCLUSIVE

No.	Age	Weight, Lbs.	Sex	P 1	P 2	P 3	Q 1	Q 2	Q 3	R 1	R 2	R 3	S 1	S 2	S 3	T 1	T 2	T 3	Rate
1	2 years	24	M	0.1	0.1	0.05	0	0.05	0.1	0.4	0.7	0.5	0	0	0	0.1	0.2	0.1	100
2	2 years	19	M	0.1	0.15	0.1	0.1	0.2	0.1	0.4	0.75	0.55	0.15	0.2	0.05	0.1	0.2	0	187
3	3½ years	31	F	0.05	0.2	0.05	0.1	0.05	0	0.3	0.5	0.2	0.1	0.3	0.1	0.2	0.4	0.1	88
4	3½ years	32	F	0.04	0.05	0.05	0.05	0.05	0	0.3	1.2	0.6	0.05	0.15	0	0.2	0.5	0.1	82
5	4 years	35	F	0.15	0.15	0.1	0.15	0.05	0.15	0.6	0.7	0.6	0	0.4	0.2	0.5	0.4	0.15*	75
6	4 years	36	M	0.1	0.3	0.06	0	0	0	0.6	1.2	0.6	0.2	0.2	0.2	0.3	0.3	0.1*	83
7	4½ years	38	F	0.1	0.3	0.2	0.1	0	0.05	0.4	0.6	0.4	0.4	0.2	0.1	0.4	0.3	0.15	100
8	5 years	47	F	0.15	0.3	0.1	0.1	0.1	?	0.5	0.6	0.2	0	0.4	0.4	0.4	0.6	0.3	82
9	5 years	49	M	0.1	0.3	0.1	0	0.1	?	0.7	0.7	0.4	0.3	0.2	0.2	0.3	0.4	0.15	105
10	5 years	40	F	0.1	0.2	0.1	0	0.1	0.05	0.7	0.8	0.5	0.1	0.2	0.3	0.2	0.2	0.3	94

TABLE 4.—TWENTY-SIX ELECTROCARDIOGRAMS OF CHILDREN AGED FROM 6 YEARS TO 13 YEARS

No.	Age, Yrs.	Weight, Lbs.	Sex	P 1	P 2	P 3	Q 1	Q 2	Q 3	R 1	R 2	R 3	S 1	S 2	S 3	T 1	T 2	T 3	Rate
1	6	41	M	0.1	0.2	0.05	0.1	0.1	0	0.6	0.8	0	0.3	0.1	0.2	0.4	0.5	0.1*	97
2	6	47	M	0.15	0.25	0.15	0.1	0.1	0.05	0.7	1.1	0.4	0	0.1	0	0.4	0.4	0.2*	100
3	6	43	F	0.1	0.05	0.1*	0.05	0.2	0	0.6	0.8	0.2	0.1	0.2	0.15	0.4	0.3	0.3*	101
4	6	42	F	0.15	0.25	0.15	0	0	0.3	0.9	2.2	2.1	0	0.1	?	0.5	0.6	0.4	100
5	6	41	M	0.1	0.2	?	0	0	?	0.5	0.7	?	0	0	?	0.4	0.3	?	95
6	7	45	F	0.2	0.2	0.1	0.1	0	0.2	0.7	0.9	0.5	0.4	0.2	0	0.7	0.5	0.4	98
7	7	47	F	0.1	0.15	0.1	0	0	0.15	0.2	0.7	0.65	0.25	0.18	0.15	0.2	0.3	0.2	100
8	7	46	F	0.05	0.2	0.2	0	0	0	0.35	0.7	0.8	0.2	0.4	0.5	0.5	0.6	0.4	80
9	8	45	F	0.1	0.15	0.05*	0	0	0	0.8	1.1	0.4	0	0.2	0.25	0.5	0.9	0.2*	101
10	8	49	F	0.1	0.2	0.1*	0.1	0	0.2	0.85	1.1	0.5	0.2	0.3	0.2	0.5	0.2	0.2	80
11	8	49	F	0.1	0.08	0.1*	0	0.1	0	0.5	1.4	0.9	0.1	0.1	0.25	0.3	0.4	0.2*	80
12	9	50	M	0.15	0.2	0.15	0.1	0.15	0.2	0.4	1.3	0.7	0.05	0.4	0.5	0.5	0.1	0.2*	98
13	10	58	M	0.1	0	0.1*	0.15	0	0	0.6	1.0	0.2	0	0.4	0.1	0.3	0.6	0.1*	98
14	10	61	M	0.1	0.15	0.15	0.1	0.1	0	0.5	1.2	0.9	0.1	0.2	0.3	0.3	0.9	0.15	82
15	10	65	M	0.15	0.1	0.1	0	0.1	0.1	1.0	1.2	0.6	0.2	0.4	0.2	0.5	0.6	0.1	88
16	11	68	M	0.1	0.1	0.1*	0	0.1	0.2	0.4	1.2	0.5	0	0.4	0.1	0.3	0.4	0.3	100
17	11	64	M	0.1	0.1	0.1*	0.15	0	0	1.0	0.8	0.4	0	0.05	0.3	0.5	0.2	0.1*	90
18	11	74	M	0.15	0.1	0.1*	0	0	0	0.5	0.5	0.1	0.1	0.2	0.1	0.3	0.2	0.1*	80
19	11	70	F	0.05	0.2	0.1	0	0.2	0.2	0.35	0.95	0.8	0.2	0.2	0.3	0.4	0.3	0.2	113
20	12	71	M	0.1	0.15	0.1	0	0	0.1	0.8	1.4	0.9	0.2	0	0.1	0.1	0.2	0.1	110
21	13	78	M	0.1	0.2	0.05	0.1	0	0.02	0.6	0.75	0.4	0.2	0.5	0	0.4	0.5	0.05	82
22	13	84	M	0.1	0.15	0.1	0	0	0.1	0.8	1.2	0.6	0	0	0	0.2	0.2	0.1	108
23	13	72	M	0.06	0.2	0	0.1	0.2	0.1	0.9	1.6	0.7	0.2	0.5	0.2	0.1	0.4	0.1	100
24	13	96	M	0.05	0.2	0.10	0	0.05	0.1	0.45	1.2	1.3	0.2	0.2	0	0.4	0.4	0.15	108
25	13	84	M	0.2	0.2	0.05	0	0.05	0	1.6	1.6	0.9	0.3	0.2	0.1	0.3	0.3	0.15	95
26	13	—	M	0.1	0.1	0.05	0.1	0	0	0.4	0.4	0.2	0.2	0.3	0.1	0.4	0.1	0.1*	78

the average for the first two years is 0.9 mm. and the average from the second to the thirteenth year is 3.4 mm. The average for the adult, according to Lewis, is 2 mm. In Lead II the T is, on the whole, higher than in Lead I. It is inconstant from month to month, and since it is so irregular, it is valueless as a guide for the normal. The average up to the second year is 1.4 mm. and during the rest of childhood it is 3.5 mm.

T_3 is still more variable. The average for the first two years is one scale division, and for the rest of childhood it is two scale divisions. The average of T_3 for the adult (according to Lewis) is 1.6 mm.

I believe that the height of the T wave is too variable to be used as a standard. It is too easily affected by all external influences. If a baby cried before being cardiographed, or for a moment during the experiment, even though it had no influence on the other deflections, it usually affected the T. That is probably the most plausible reason for the high peaks seen in Figure 6 at periods when there were no physiologic causes; as in Lead I at 4 months and at 1 year; in Lead II at 3 months and at 7 years; in Lead III at 3 months and 6 years.

The T was found inverted rather rarely. It was normal in all leads of all ages, except in Lead III between 6 and 13 years, during which period it was inverted in 15 per cent.

Rate and Rhythm.—There exists a general clinical impression among pediatrists that the pulse of the normal child is more susceptible to changes in rate and rhythm than is that of the adult, that in the new-born, and the infant especially, the pulse is so variable that it is difficult to establish a normal standard, and that arrhythmias occur much more frequently in the new-born and the nursling than in later childhood. I was unable to confirm these opinions by a study of the tracings of hearts of normal children with the electrocardiograph. I found, on the contrary, that the younger the child, the faster is the pulse rate, and that the faster the pulse rate the less frequently arrhythmias occurred. The electrocardiograms in this study were all obtained under exactly similar conditions. In the case of nurslings the readings were taken at the same time of day, right after the feeding, and in older children at about 10 a. m.

The fact that the nurslings were fed before the reading might account for the rather high pulse rates obtained in Tables 5 to 8. The average of from seven to ten pulse periods was taken from each tracing. The time interval for each pulse period was recorded in fiftieths of a second.

Tables 5 to 8, following Krumbhaar, irregularities showing a difference of more than 0.1 of a second, between the shortest and longest

heart cycle, were considered as evidence of sinus arrhythmia. In the new-born I found the average difference between the highest and lowest pulse periods 0.04 second (Table 5). Hecht and Krumbhaar found that at this period the average difference was 0.12 and 0.04 second, respectively. From 6 to 13 years, the figures of Hecht and Krumbhaar are respectively 0.16 and 0.10 second.

TABLE 5.—PULSE PERIOD AND RATE OF NORMAL NEW-BORNS

No.	Age	Sex	Weight, Gm.	Pulse Period	Small-est	Larg-est	Arith-metical Aver-age	Dif-fer-ence	Pulse Rate
1	24 hours	M	3,600	15–15–15–15–15 15–15–15–15–15	15	15	15.0	0	210
2	24 hours	F	2,840	20–20–20–22–20 24–22–20–22–20	20	24	21.0	4	152
3	2 days	M	3,230	35–33–33–30–29 29–29–28	28	35	30.6	7	102
4	2 days	F	2,940	19–20–20–20–20 20–21–21	19	21	20.1	2	159
5	3 days	M	3,250	20–20–19–20–21 20	19	21	16.6	2	158
6	6 days	F	3,440	17–17–17–17–17 17–18–18–18–17	17	18	17.3	1	160
7	5 days	M	3,420	15–15–15–15–15 15–15–15–15–15	15	15	15.0	0	210
8	4 days	M	3,810	19–20–18–18–18 19–18–19–19	18	20	18.7	2	158
9	6 days	F	3,440	22–24–23–23–23 24–24–23	22	24	23.2	2	150
10	7 days	F	4,000	23–23–24–25–24 24–24–24	23	25	23.8	2	132
11	7 days	F	3,115	27–25–28–27–27	25	28	26.8	3	118
12	7 days	M	3,430	18–18–18–18–18 18–18–19–18–18	18	19	18.1	1	160
13	11 days	M	3,545	20–19–20–20–19	19	20	19.6	1	158
14	9 days	M	3,900	23–24–25–24–23 23–23–24–25–24	23	25	23.8	2	135
15	9 days	M	3,900	17–18–17–18–18 17–18–17–17–18	17	18	17.5	1	180

Average pulse rate, 157.
Average pulse period, 20.4 (in 1/50 second).
Average difference between highest and lowest pulse period, 1.0 (in 1/50 second).

Although there is a slight difference in the exact time interval in our three studies, nevertheless, the general impression that arrhythmias are more frequent in new-borns than in older children is controverted by all. In general, the pulse rate decreases with age, and with this decrease arrhythmias become more frequent. In the new-born, there was only one case of sinus arrhythmia with a difference of 0.14 second (Table 5, No. 3). In the next group (from 11 days to 1 year) the highest irregularity was 0.10 second (Table 6). In the next group (from 1 to 5 years), there was only one instance in which the differ-

TABLE 6.—Pulse Period and Rate of Normal Nurslings Aged from 11 Days to 1 Year

No.	Age	Sex	Weight, Gm.	Pulse Period	Smallest	Largest	Arithmetical Average	Difference	Pulse Rate
1	6 weeks	M	4,200	19.5–19.5–19.5–19.5–19.5 19.5–19.5–19.5–19.5	19.5	19.5	19.5	0	132
2	6 weeks	M	3,900	21–21–21–22.5–21–21 20–20–20	20.0	22.5	20.8	2.5	144
3	6 weeks	M	4,120	18.7–18.7–18.7–18.7–18.7 18.7–18.7–18.7–18.7–18.7	18.7	18.7	18.7	0	165
4	6 weeks	F	4,100	22.5–23–20.5–21.5–21.5 20.5–22–22–22–24	21.5	24.0	22.0	2.5	144
5	7 weeks	M	4,230	19–19–19–19–19–19–20 20–20–20	19.0	20.0	19.4	1.0	150
6	2 mos.	F	4,330	24–24–24–24–24–24–24 24–24–25	24.0	25.0	24.1	1.0	120
7	2 mos.	F	4,500	26–25.5–25.5–25–25–25 25–23.5	23.5	26.0	25.0	2.5	125
8	2 mos.	M	4,120	23–23–23–23–23	23.0	23.0	23.0	0	135
9	2 mos.	M	4,020	16–16–16–16–16–16–16 16–16–16	16.0	16.0	16.0	0	182
10	7 weeks	F	4,230	20–20–20–20–20–20–20.5 20–20–20	20.0	20.5	20.0	0.5	145
11	74 days	M	3,720	19–20–20–20–20–21.5–24 24–24	19.0	24.0	23.7	5.0	144
12	8 mos.	M	8,100	23.5–23.5–23.5–23.5–23.5 23.5–23.5–23–23–23	23.0	23.5	23.4	0.5	128
13	....	..	.....	20.5–20.5–20.5–20.5–20.5 20.5–20.5–20.5–20.5–20.5	20.5	20.5	20.5	0	145
14	10 mos.	F	9,000	20–20.5–20.5–20.5–20.5 20.5–20.5–21–21–21	20.5	21.0	20.6	0.5	150
15	11 mos.	M	8,560	26–26–26–26–23.5–28.5 28.5	26.0	28.5	27.0	2.5	117
16	11 mos.	F	8,900	24–24–24–24–24–24–24 24–24–25	24.0	25.0	24.1	1.0	135
17	3½ mos.	F	5,850	24–23–23–23–23–23–24	23.0	24.0	23.2	1.0	132
18	4 mos.	F	6,120	26–26–26–26–26–26–26 26–26	26.0	26.0	26.0	0	118
19	5 mos.	M	4,220	21.5–21.5–21.5–21.5–21.5 21.5–21.5–21.5	21.5	21.5	21.5	0	135
20	5½ mos.	M	4,800	30–29.5–29.5–29.5–29.5 29.5	29.5	30.0	29.6	0.5	126
21	6 mos.	M	5,100	24–22.5–22.5–22.5–22.5–22.5 22.5–22.5–22.5–22.5	22.5	24.0	22.8	1.5	135
22	11 mos.	F	7,650	19–18.8–18.8–18.8–18.8–18.8 18.8–19.5–19.5–19.5	18.8	19.5	19.0	0.7	168
23	11 mos.	F	8,345	27–27–27–27–27–27–27–28.5	27.0	28.5	27.2	1.5	106

Average pulse period, 22.5 (in $1/50$ second).
Average pulse rate, 138.
Average difference between highest and lowest pulse period, 1.0 (in $1/50$ second).

ence was 0.08 second (Table 7). In schoolchildren, however, (from 6 to 13 years) 47 per cent. showed an arrhythmia over 0.10 second (Table 8).

Transmission Time.—In order to interpret an electrocardiogram correctly, one must first know what constitutes the normal variations in the auricular and ventricular conduction time in children of all ages. In order to establish such a normal standard, I measured the P R interval (auricular activity), the R T interval (ventricular activity) which includes the Q R S and S T intervals, the T P interval (diastolic phase) and the P P interval which represents the complete heart cycle. I then calculated the ratio in the percentages between the three phases of the heart cycle, the P R, the R T, the T P, and the entire heart cycle, the P P.

TABLE 7.—PULSE PERIOD AND RATE OF NORMAL CHILDREN
AGED FROM 2 TO 5 YEARS

No.	Age	Sex	Weight, Lbs.	Pulse Period	Small-est	Larg-est	Arith-metical Aver-age	Dif-fer-ence	Pulse Rate
1	13 mos.	M	21	24–22.5–22.5–21–21–20.5 20.5–20.5–20.5–22.5	20.5	24.0	21.5	4.0	144
2	14 mos.	M	24	31–29–28–30–30–30	28.0	31.0	29.6	3.0	105
3	14 mos.	M	26	22–22–22–22–22–22 22–22–22	22.0	22.0	22.0	0	135
4	15 mos.	F	22	28–28–28–28–28–28–27.5 27.5–27.5–26.5	26.5	28.0	27.7	1.5	108
5	15 mos.	F	23	24.5–25.5–25.5–26–27.5 29–25.5–29–29	24.5	29.0	26.6	4.5	108
6	16 mos.	F	24	25–24–29–29–22.5–22.5 22.5–23–24–24	22.5	25.0	23.5	2.5	135
7	19 mos.	F	27	20–20–20–20–20–20 20–20–20.5	20.0	20.5	20.0	0.5	145
8	2 years	F	28	15.5–15.5–15.5–15.5–15.5 15.5–15.5–15.5–15.5	15.5	15.5	15.5	0	190
9	2 years	F	26	20–20.5–20–20–20–20.5 20.5–20.5	20.0	20.5	20.3	0.5	120
10	2 years	F	25	21–21–21–21–21–21 21–21–20	20.0	21.0	20.9	1.0	144

Average pulse rate, 133.
Average pulse period, 22.7 (in 1/50 second).
Average difference between highest and lowest pulse period, 1.75 (in 1/50 second).

P R Interval.—In the new-born the auricular impulse is shorter than at any later period. It is also remarkably constant, averaging 0.113 second. The longest period was in a baby, 4 days old, 0.15 second, and the shortest 0.09 second. The average obtained from the percentage calculated from each of the tracings is 27.7 per cent. The average obtained from these averages is 26.91, a difference of a little over 1 per cent. (Table 9).

TABLE 8.—Pulse Period and Rate of Normal Children Aged from 6 to 13 Years

No.	Age	Sex	Weight, Lbs.	Pulse Period	Small-est	Larg-est	Arith-metical Aver-age	Dif-fer-ence	Pulse Rate
1	3½ years	M	35	35–31.5–31.5–33.5–33.5 32–30–31	30.0	35.0	32.2	5.0	85
2	4½ years	M	38	35.5–37–37.5–37	35.5	37.5	36.6	2.0	84
3	6 years	F	42	33.8–32–20–28–28–30–30	28.0	33.8	30.2	5.8	105
4	6 years	M	44	31–30–31.6–33–33–32	30.0	33.0	31.7	3.0	96
5	6 years	F	39	33–36–32–31–30–34–34 34–35	30.0	36.0	33.1	6.0	105
6	6 years	F	37	40–35–31–32–35.5–35.5	31.0	40.0	34.8	9.0	84
7	7 years	M	44	39–40.5–37.5–39–35.5	35.5	40.5	38.5	5.0	82
8	7 years	M	45	33–33–33–33–34–34–33 33–33–33	33.0	34.0	33.2	1.0	96
9	7 years	M	47	34–35–35–41–40–40.5	34.0	41.0	37.6	7.0	84
10	7 years	F	46	32.5–29.5–30.5–34–34 30.5	29.5	34.0	31.7	4.5	96
11	8 years	F	51	36–37.5–37.5–37.5–37.5–37.5 37.5–35.5–37.5–37.5	35.5	37.5	37.1	2.0	99
12	11 years	F	75	27.5–27.5–27.5–27.5–27.5 27.5	27.5	27.5	27.5	0	108
13	8 years	F	50	42–39–42–36.5–44–44.5	36.5	44.5	41.3	8.0	75
14	9 years	M	59	29–31–34–33–30–31.5–37 30.5	29.0	37.0	32.0	8.0	96
15	11 years	M	78	26.5–26.5–26.5–26–26–26	26.0	26.5	26.3	0.5	108
16	11 years	M	76	36–35–36–34.5	34.5	36.0	35.4	1.5	84
17	11 years	M	68	25.5–25.5–25.5–25.5–25.5 26.5–26.5–29–29.5	25.5	29.5	26.5	4.0	115
18	13 years	F	85	29–28–28–28–28–28–28	28.0	29.0	28.1	1.0	108
19	13 years	F	81	30.5–39–35–31.5–31.5–31–35	30.5	39.0	33.3	8.5	80

Average pulse rate, 83.6.
Average pulse period, 33.0 (in 1/50 second).
Average difference between highest and lowest pulse period, 4.3 (in 1/50 second).

TABLE 9.—Transmission Time of Normal New-Borns

Nc.	Age	P R	R T	T P	P P	Percentage			Pulse Rate
						P R to P P	R T to P P	T P to P P	
1	10 days	0.10	0.23	0.27	0.60	16.6	38.33	45.0	100
2	2 days	0.111	0.21	0.08	0.40	27.5	52.50	20.0	150
3	16 hours	0.12	0.20	0.05	0.37	23.4	54.05	13.5	157
4	24 hours	0.112	0.23	0.05	0.40	30.0	57.5	12.5	152
5	4 days	0.15	0.22	0.08	0.45	33.3	48.88	17.5	135
6	9 days	0.12	0.20	0.03	0.35	34.3	57.14	8.57	174
7	18 hours	0.11	0.19	0.10	0.40	27.5	47.5	25.0	150
8	5 days	0.10	0.21	0.10	0.41	24.3	51.22	24.19	135
9	3 days	0.09	0.21	0.09	0.39	23.3	53.85	23.33	150
Average........		0.113	0.211	0.94	0.419	27.7	50.07	21.10	144.8
Average percentage calculated from the averages........						26.9	50.36	22.43	

In the next period (from 11 days to 1 year) the P R interval averages slightly longer (0.125 second). The shortest period is 0.10 and the longest 0.18 second. The P P ratio is 29.34 and 28 per cent., respectively (Table 10). From the first to the fifth year the P R interval is slightly less than in the previous period (0.123), the lowest being 0.10 and the highest 0.16 second. The auricular impulse at this age constitutes from 24.11 to 24.50 per cent. of the entire heart cycle (Table 11).

TABLE 10.—TRANSMISSION TIME OF NORMAL NURSLINGS
AGED FROM 11 DAYS TO 1 YEAR

No.	Age	P Q	Q R S	S T	T P	P P	Percentage				Pulse Rate
							P R to P P	Q R S to P P	S T to P P	T P to P P	
1	4 wks.	0.11	0.03	0.19	0.03	0.36	30.5	8.40	52.77	8.33	164
2	6 wks.	0.13	0.03	0.22	0.07	0.45	28.9	6.67	48.88	15.55	144
3	6 wks.	0.10	0.04	0.21	0.09	0.44	22.7	9.45	47.73	20.45	144
4	6 wks.	0.12	0.04	0.19	0.05	0.40	35.1	4.9	47.5	12.50	157
5	6 wks.	0.12	0.03	0.20	0.05	0.40	32.5	5.00	50.0	12.5	157
6	7 wks.	0.11	0.03	0.21	0.05	0.40	27.5	7.50	52.5	12.5	150
7	11 mos.	0.13	0.04	0.20	0.07	0.42	30.9	4.91	47.62	16.57	135
8	2 mos.	0.12	0.04	0.20	0.08	0.43	27.9	6.99	46.51	18.60	140
9	2 mos.	0.11	0.02	0.18	0.04	0.35	31.4	5.76	51.42	11.42	180
10	4 mos.	0.12	0.02	0.22	0.11	0.47	25.5	4.30	46.8	23.40	132
11	5 mos.	0.15	0.03	0.24	0.04	0.46	32.6	6.54	52.17	8.69	135
12	5½ mos.	0.12	0.04	0.21	0.09	0.48	25.0	12.50	43.75	18.75	126
13	6 mos.	0.13	0.05	0.21	0.04	0.43	30.2	11.67	48.83	9.30	135
14	8 mos.	0.12	0.02	0.21	0.13	0.48	25.0	4.17	43.75	27.08	126
15	10 mos.	0.12	0.04	0.24	0.05	0.45	26.6	8.96	53.33	11.11	135
16	11 mos.	0.18	0.05	0.22	0.10	0.55	38.9	2.92	40.00	18.18	98
17	11 mos.	0.14	0.05	0.27	0.06	0.52	26.9	9.64	51.92	11.54	117
18	14 mos.	0.12	0.04	0.18	0.06	0.40	30.0	10.00	45.00	15.0	150
	Average...	0.125	0.036	0.211	0.067	0.44	29.34	7.24	48.36	15.19	133.3
	Average percentage calculated from the averages..						28.0	8.18	47.28	15.22	

TABLE 11.—TRANSMISSION TIME OF NORMAL CHILDREN AGED
FROM 1 YEAR TO 5 YEARS

No.	Age	P Q	Q R S	S T	T P	P P	Percentage				Pulse Rate
							P R to P P	Q R S to P P	S T to P P	T P to P P	
1	13 mos.	0.11	0.04	0.20	0.10	0.45	24.44	8.88	44.44	22.22	135
2	12 mos.	0.11	0.04	0.22	0.11	0.48	22.91	8.33	45.81	22.91	132
3	12 mos.	0.10	0.04	0.22	0.22	0.58	17.24	6.89	37.93	37.93	105
4	14 mos.	0.11	0.07	0.20	0.08	0.46	23.93	15.21	43.47	17.38	125
5	15 mos.	0.12	0.04	0.22	0.20	0.58	20.69	6.89	37.93	34.48	108
6	15 mos.	0.11	0.05	0.25	0.11	0.52	21.15	9.61	48.07	21.15	108
7	16 mos.	0.13	0.04	0.20	0.08	0.45	28.88	8.88	44.44	17.77	135
8	19 mos.	0.11	0.04	0.20	0.20	0.55	20.0	7.27	36.36	36.36	108
9	19 mos.	0.11	0.06	0.20	0.03	0.40	27.5	15.0	50.0	17.5	145
10	2 yrs.	0.12	0.04	0.18	0.08	0.42	28.57	9.52	61.94	19.45	142
11	2 yrs.	0.11	0.06	0.17	0.05	0.39	28.20	15.38	43.59	12.82	158
12	2 yrs.	0.16	0.035	0.22	0.08	0.49	32.65	7.14	44.89	16.32	119
13	3½ yrs.	0.16	0.07	0.23	0.18	0.64	25.0	10.98	35.93	28.12	95
14	4½ yrs.	0.16	0.07	0.28	0.22	0.73	21.92	9.59	38.35	30.13	88
	Average...	0.123	0.049	0.213	0.125	0.51	24.50	9.97	43.79	23.19	122.3
	Average percentage calculated from the averages..						24.11	9.61	41.76	24.51	

TABLE 12.—Transmission Time of Normal Children Aged from 6 to 13 Years

No.	Age	P Q	Q R S	S T	T P	P P	Percentage P R to P P	Percentage Q R S to P P	Percentage S T to P P	Percentage T P to P P	Pulse Rate
1	6 yrs.	0.12	0.04	0.28	0.11	0.55	21.8	7.27	50.9	20.0	108
2	6 yrs.	0.14	0.06	0.26	0.14	0.60	23.3	10.0	43.3	23.3	100
3	6 yrs.	0.13	0.07	0.30	0.17	0.67	19.4	10.4	44.7	25.3	90
4	7 yrs.	0.16	0.08	0.31	0.18	0.73	21.9	10.9	41.6	24.7	82
5	7 yrs.	0.18	0.08	0.26	0.12	0.64	28.1	12.5	40.6	18.7	95
6	7 yrs.	0.16	0.06	0.26	0.12	0.60	26.6	10.0	43.3	20.0	96
7	7 yrs.	0.14	0.07	0.27	0.09	0.57	24.5	12.2	47.3	15.7	100
8	8 yrs.	0.12	0.08	0.28	0.30	0.78	15.3	10.2	36.2	38.4	72
9	8 yrs.	0.11	0.08	0.28	0.26	0.73	15.0	10.9	38.3	35.6	80
10	9 yrs.	0.12	0.06	0.27	0.22	0.67	17.9	8.9	40.2	35.8	95
11	10 yrs.	0.12	0.07	0.29	0.06	0.54	22.2	12.9	53.5	11.1	105
12	10 yrs.	0.11	0.06	0.29	0.20	0.66	16.6	9.0	43.9	30.3	90
13	11 yrs.	0.14	0.06	0.24	0.07	0.51	27.4	11.7	47.0	13.7	110
14	11 yrs.	0.12	0.08	0.26	0.05	0.51	23.5	15.6	50.9	9.8	112
15	11 yrs.	0.18	0.08	0.26	0.18	0.70	25.7	11.4	37.1	25.7	84
16	12 yrs.	0.15	0.06	0.27	0.06	0.54	27.7	11.1	50.0	11.1	108
17	13 yrs.	0.13	0.08	0.24	0.09	0.54	24.0	14.8	44.4	16.6	108
18	13 yrs.	0.17	0.08	0.30	0.08	0.63	26.9	12.6	47.6	12.6	95
	Average...	0.138	0.069	0.273	0.139	0.620	22.6	11.2	44.4	21.5	961
	Average percentage calculated from the averages..						22.25	11.13	44.03	22.41	

TABLE 13.—Weight of the Musculature of the Left and Right Ventricles in Grams

Boys Left	Boys Right	Girls Left	Girls Right	Age	Boys: L.R. Index	Girls: L.R. Index
3.51	3.8	.....	.....	Fetus 8 mos.	0.92	
5.04	4.35	4.33	3.62	Fetus 9 mos.	1.1	1.1
8.14	6.54	7.95	6.47	Newborn.............	1.2	1.2
12.07	7.23	10.92	6.81	1 to 2 mos.	1.7	1.6
18.13	9.13	16.72	8.61	5 to 6 mos.	2.0	2.0
24.48	12.47	23.49	11.82	11 to 12 mos.	2.0	2.11
29.29	15.92	28.15	14.65	1 to 2 years.........	1.84	1.92
38.51	18.16	36.25	17.69	3 to 4 years.........	2.12	2.05
44.98	23.48	43.07	20.24	5 to 6 years.........	1.97	2.13
49.94	23.33	45.83	23.39	6 to 7 years.........	2.14	1.95
52.25	25.08	48.36	23.39	7 to 8 years.........	2.08	2.06
54.29	26.62	50.76	24.72	8 to 9 years.........	2.04	2.07
57.74	27.7	50.51	26.62	9 to 10 years........	2.08	1.97
60.39	30.12	59.83	28.54	10 to 11 years.......	2.04	2.10
66.98	32.21	67.3	33.92	11 to 12 years.......	2.79	1.99
72.87	38.0	73.1	36.98	12 to 13 years.......	1.92	1.98
95.45	41.76	93.2	43.7	13 to 14 years........	2.04	2.13

TABLE 14.—Thickness of the Walls of the Right and Left Ventricles

Author	Age	Right Ventricle	Left Ventricle	L.R. Index
Bednar..	Fetus 3 mos.	1.5	1.0	0.66
Bednar..	Fetus 6 mos.	4.0	3.0	0.75
Bednar..	Birth	0.44–0.68	0.34–0.44	0.75–0.65
Bednar..	Newborn	4.0	4.0	1.0
Falk...	Newborn	0.27	0.42	1.55
Gillepsie.....................................	Newborn	4.0	3.0	0.75
Gillepsie.....................................	Newborn	5.0	5.0	1.0
Gibson..	Newborn	4.0	4.0	1.0
Bednar..	1 month	3.2	5.4	1.68
Gibson..	1 month	3.2	5.4	1.68
Gibson..	2–3 months	2.6	6.0	2.31
Gibson..	4–5 months	3.0	6.5	2.17
Bednar..	5 months	3.0	6.5	2.17
Falk...	5–6 months	2.7	5.2	1.92
Gibson..	6–8 months	2.3	6.8	2.95
Gillepsie.....................................	11 months	2.0	5.0	2.5
Gibson..	9–12 months	3.4	8.1	2.38
Gillepsie.....................................	22 months	2.0	8.0	4.0
Notori..	2–9 years	3.4–8.1	8.1	2.38
Notori..	10–20 years	4.0	1.0	2.50

In the last period of childhood (from 6 to 13 years) the P R interval averages 0.138 second. The shortest and the longest intervals are 0.11 and 0.18 second, respectively. The conduction time is from 22.25 to 22.6 per cent. of the entire pulse period (Table 12).

R T Interval.—The R T interval is composed of the Q R S and the S T periods. The Q R S includes from the beginning of Q, wherever present, to the end of S. The S T is from the end of S to the end of T. In the new-born, on account of the frequent absence of the Q, the R T was calculated as a whole. During the first ten
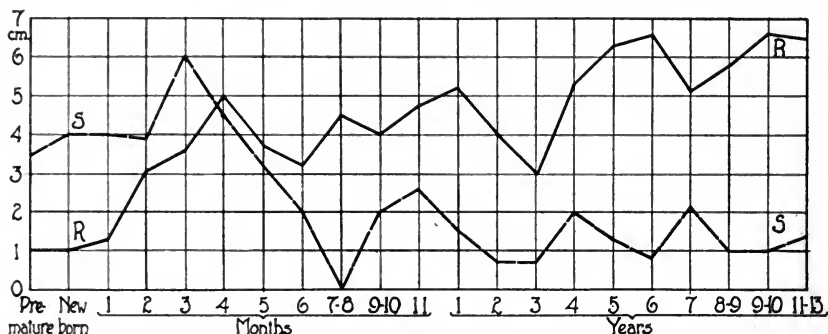
Fig. 7.—Comparison of R_1 and S_1 in all ages. Each square represents 0.5 mlvt. or 5 scale divisions.
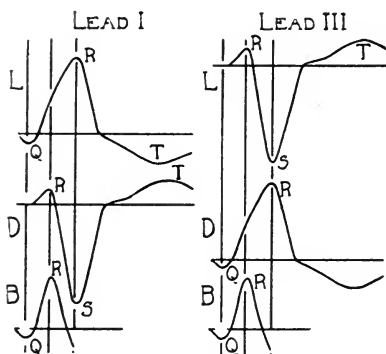
Fig. 8.—Schematic diagram of levogram, dextrogram and bigram (taken from Lewis: Clinical Electrocardiography).

days of life, the period of ventricular activity as thus measured is from 50.07 to 50.36 per cent. of the heart cycle, a little less than twice the auricular activity. It measures 0.211 second, the lowest and the highest being 0.19 and 0.23 second, respectively (Table 9). In the next age (from 11 days to 1 year) the R T phase is somewhat longer. Both the R R S and S T can be recognized, the Q R S averaging 0.036, the S T 0.211, and totaling 0.247 second. The shortest Q R S time is 0.02 and the longest 0.05. It is quite constant in all
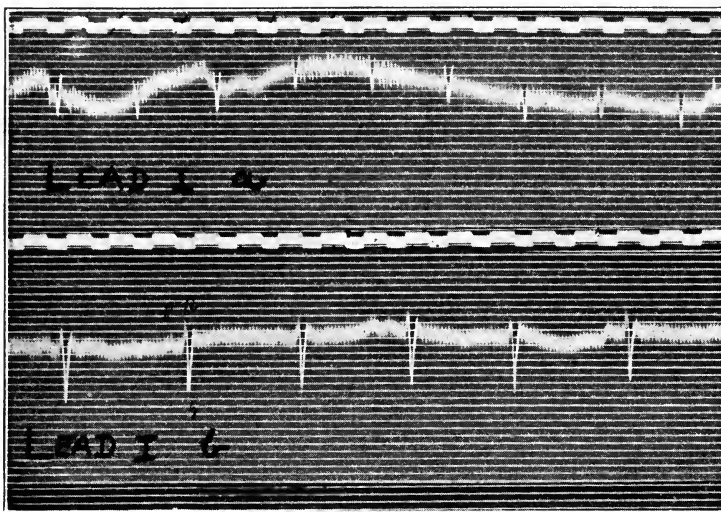
Fig. 9.—Effect of nursing new-born on electrocardiogram: (a) before nursing; (b) after nursing. Lead I only.
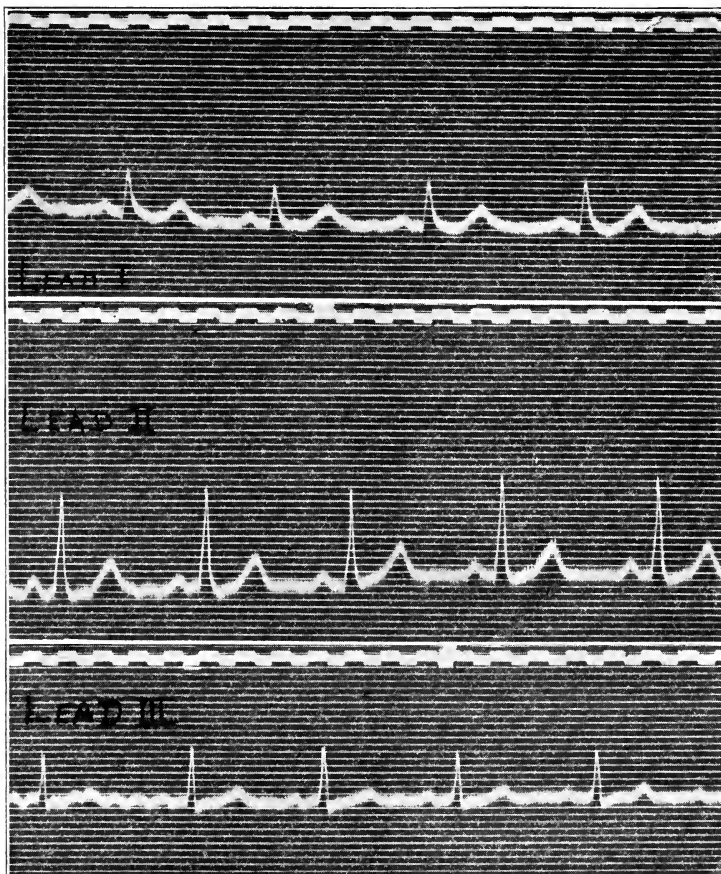
Fig. 10.—Effect on electrocardiogram of change of position: Patient recumbent.

readings. The S T averages 0.211 second. The shortest and the longest intervals are 0.18 and 0.24 second, respectively. The Q R S P P ratio is 7.24 to 8.18 per cent. and the S T : P P ratio is from 47.28 to 48.36 per cent. (Table 10).

In the next period (from 1 to 5 years), the Q R S interval averages 0.049 second and ranges from 0.035 to 0.07 second. It comprises from 9.61 to 9.97 per cent. of the entire heart cycle.
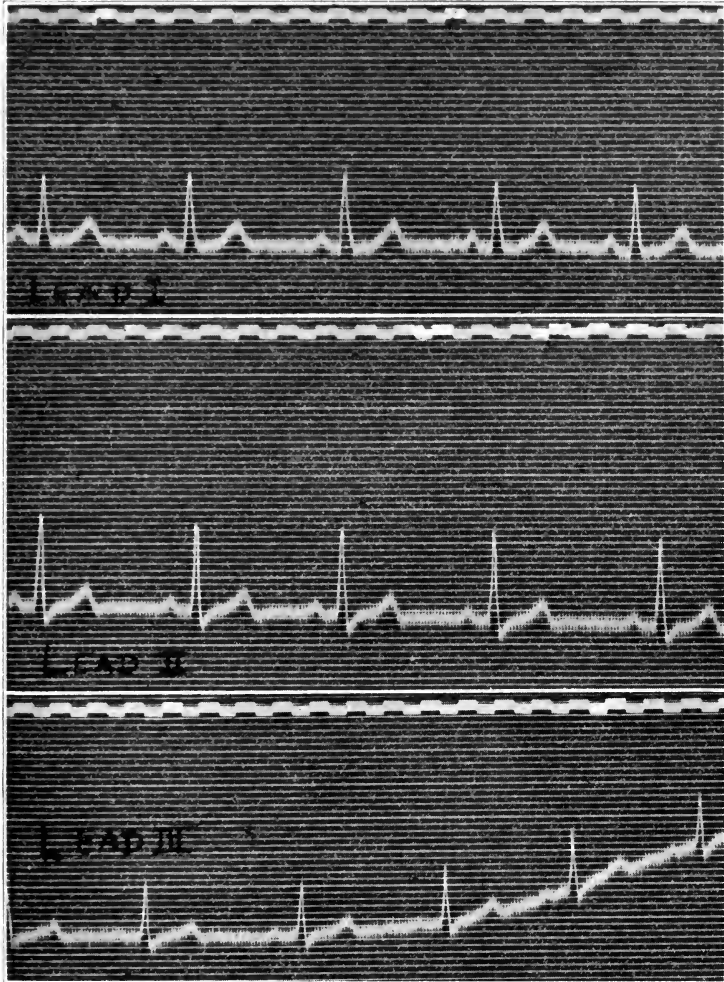
Fig. 11.—Effect on electrocardiogram of change of position: Patient seated.

The S T averages 0.213 second, and ranges from 0.17 to 0.28 second. It is from 41.76 to 43.79 per cent. of the pulse period. The total Q T interval during this period averages 0.262 and is about 51 per cent. of the pulse period (Table 11).

The Q S interval during the latter part of childhood averages 0.069 second and ranges from 0.04 to 0.08 second. The S T averages 0.273 second and ranges from 0.24 to 0.31 second. The Q R S : P P ratio is 11.2 per cent., and the S T : P P ratio is 44.2. per cent. The total Q T interval averages 0.342 second and the total Q T : P P ratio is 55 per cent. The average Q T in the adult is 0.36 second (Q R S 10) and (S T 0.26 second) (Table 12). With the exception of the S T during the latter part of childhood, the duration of both auricular and ventricular conduction time is less than in the adult.
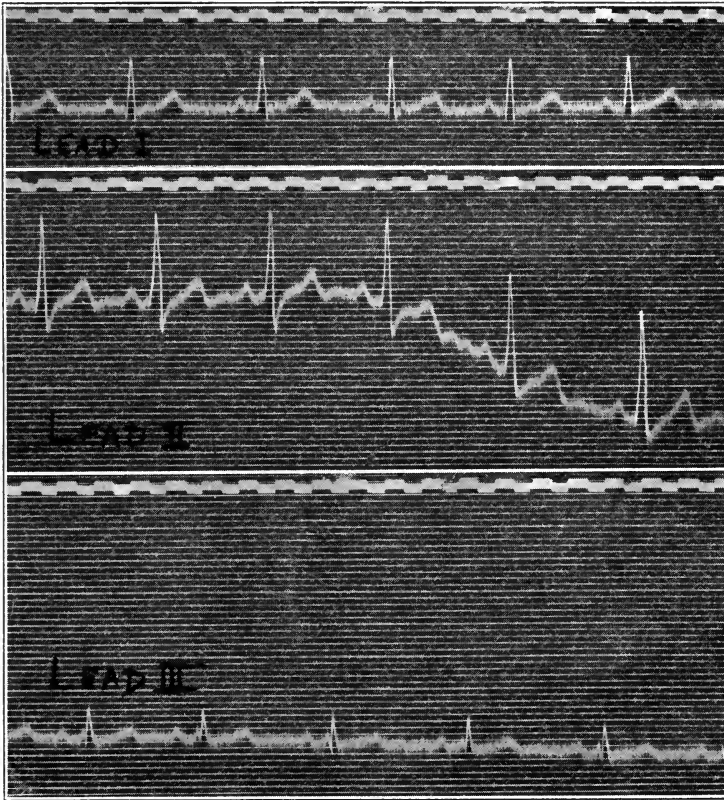
Fig. 12.—Effect of change of position on electrocardiogram: Patient lying on right side.

T P Interval.—The T P interval represents the period of rest. Obviously it depends on the pulse rate, and is so variable and inconstant that it is useless as a guide for the normal.

Ventricular Preponderance.—Lewis [23] defines ventricular preponderance as the disturbed weight ratio between the two ventricles. This may be due to pathologic changes, as in heart disease, or it may be an entirely physiologic phenomenon, as in the normal growth of the

heart during and through childhood. It is difficult many times, particularly in the infant, to decide clinically whether a hypertrophy exists. In such an instance the electrocardiograph is especially valuable.
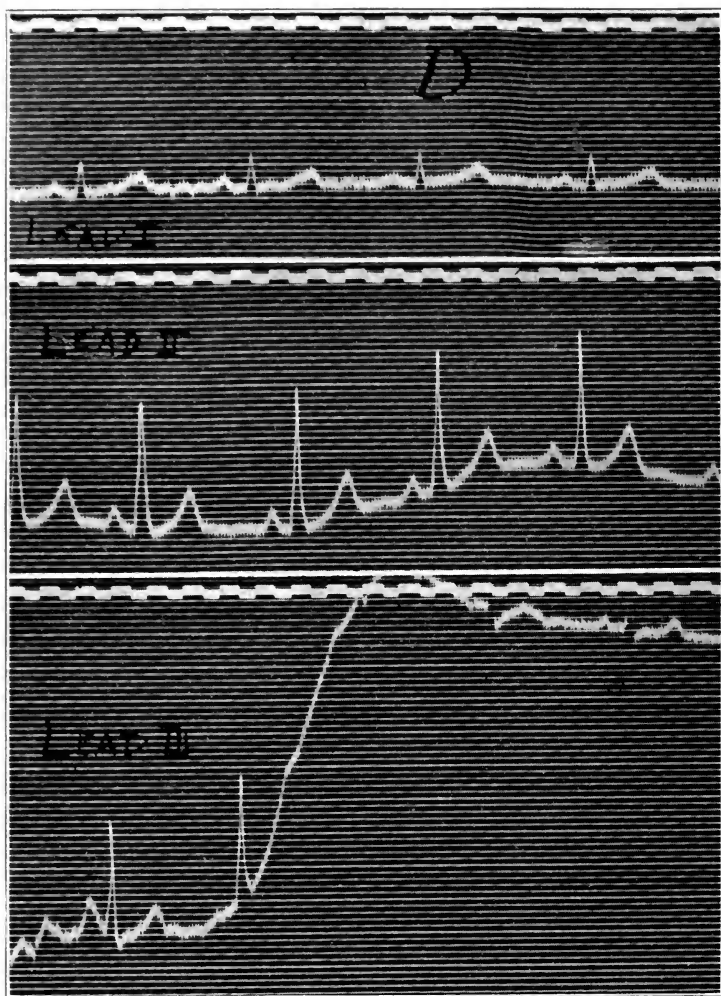
Fig. 13.—Effect of change of position on electrocardiogram: Patient lying on left side.

Figure 8 (taken from Lewis) is a schematic diagram of the separate curves of each ventricular phase in each lead. In the upper curve (1) the right division of the bundle which transmits impulses through the ventricle is severed below its origin, and the normal impulse no longer travels through it but instead spreads itself through the left branch. Lewis terms this levogram.

The middle curve (D), termed the dextrogram, represents the opposite condition in which the impulse passes only through the right ventricle branch and the left ventricle branch is severed. The lowest curve is the "bigram" and represents the algebraic sum of the other two.

All observers are agreed that in the premature, in the new-born, and for a short time thereafter, there is a definite and characteristic
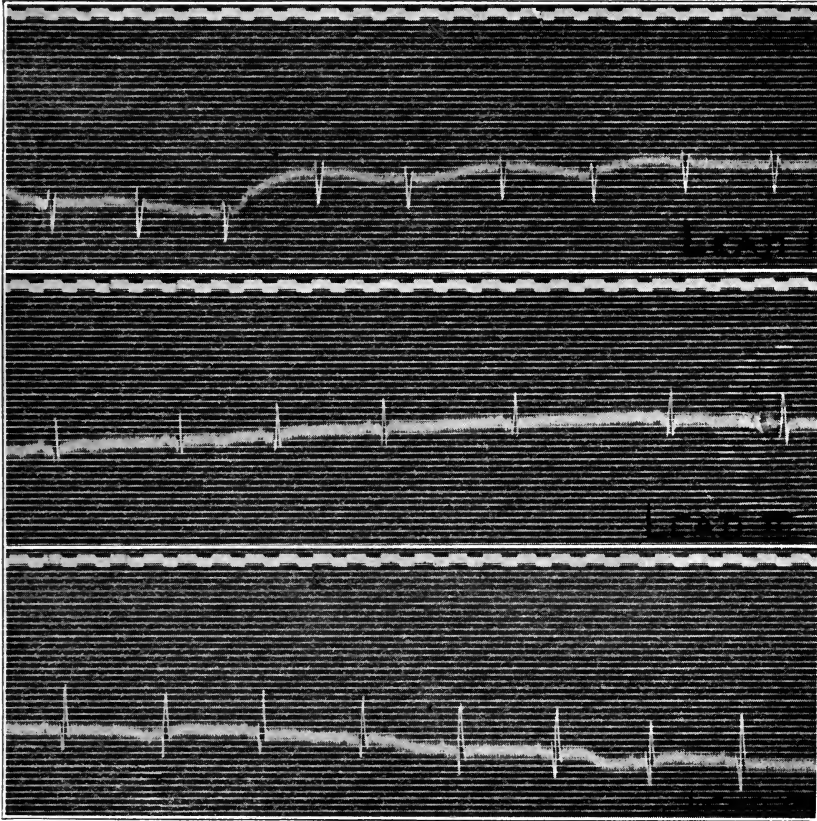
Fig. 14.—Electrocardiogram of normal new-born 24 hours old.

electrocardiogram which in form and height of deflection is entirely different from that of the older child and that of the adult. Funaro, in 1908, under the direction of Nicolai, first observed this cardiogram. He concluded that it represented a left ventricular preponderance. The anatomic data in our possession at the present time contradict this opinion. Heubner, Noeggerath[14] and others also noted this peculiar type of curve in the new-born. They explained it by the high position of the diaphragm, and consequently the more horizontal axis of the

heart. This theory could not be confirmed by the electrocardiograms which I obtained from subjects lying either on their left or right sides. In these instances although the height of the deflections changed in the different positions the outline of the curve remained essentially the same (Figs. 9, 10, 11, 12 and 13).
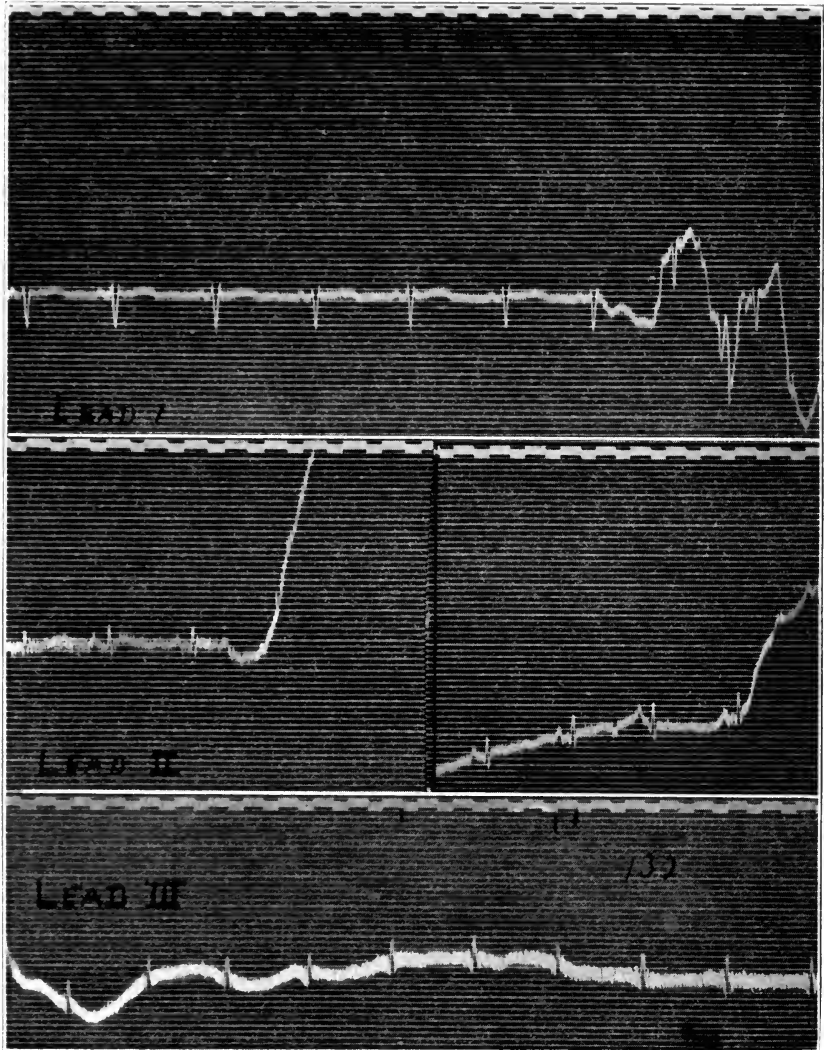
Fig. 15.—Electrocardiogram of normal new-born 48 hours old.

What effect do the muscle mass, the thickness of the walls, and the weight of the ventricle have on the electrocardiogram? A careful study (Tables 13 and 14) of the anatomic data obtained from dis-
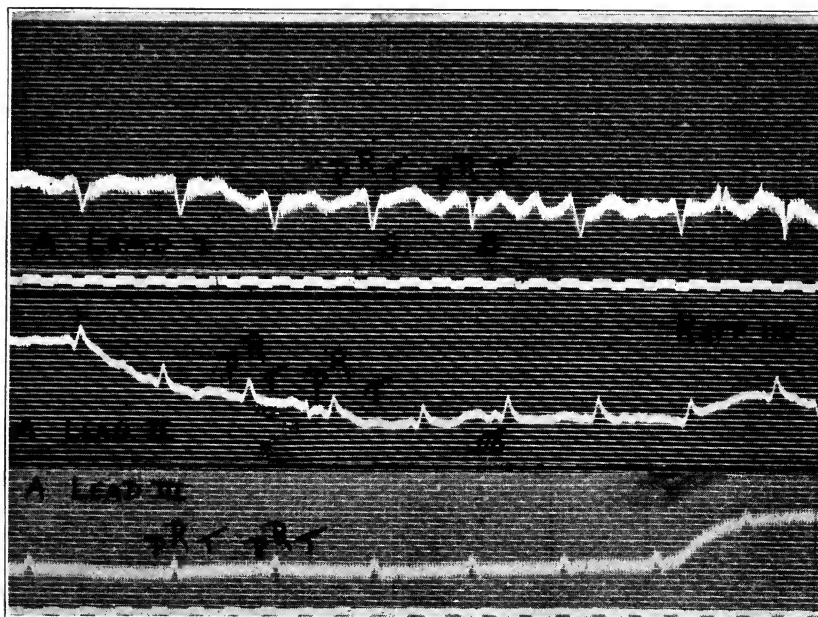
Fig. 16.—Electrocardiogram of a new-born 4 hours old.
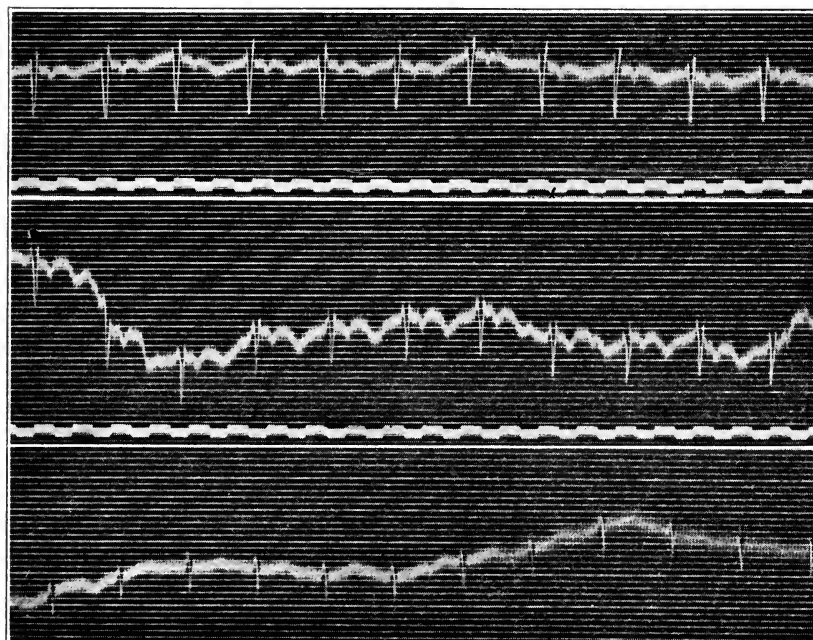
Fig. 17.—Electrocardiogram of the same new-born (Fig. 16) 4 weeks old.
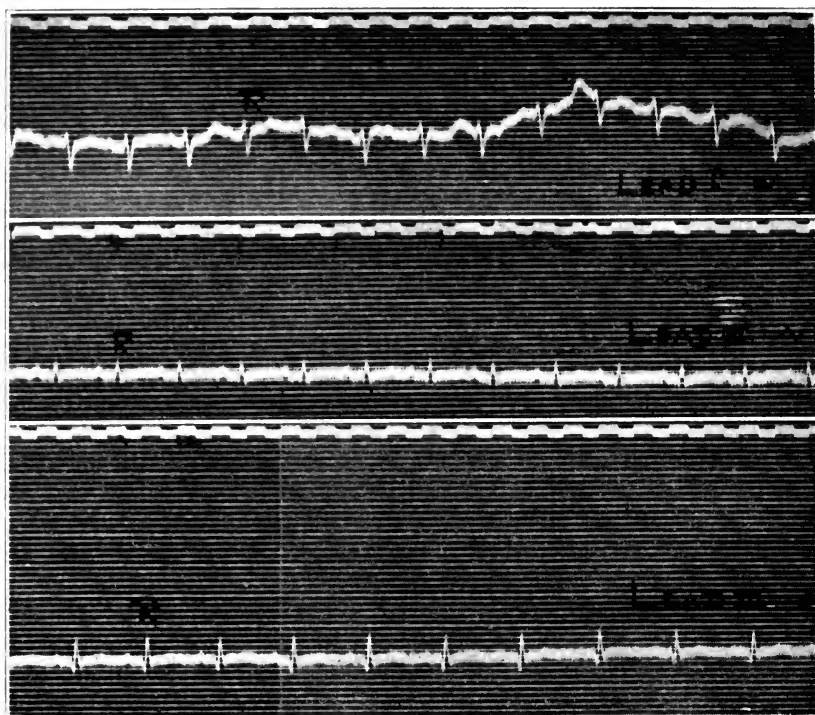
Fig. 18.—Electrocardiogram of new-born 5 days old.
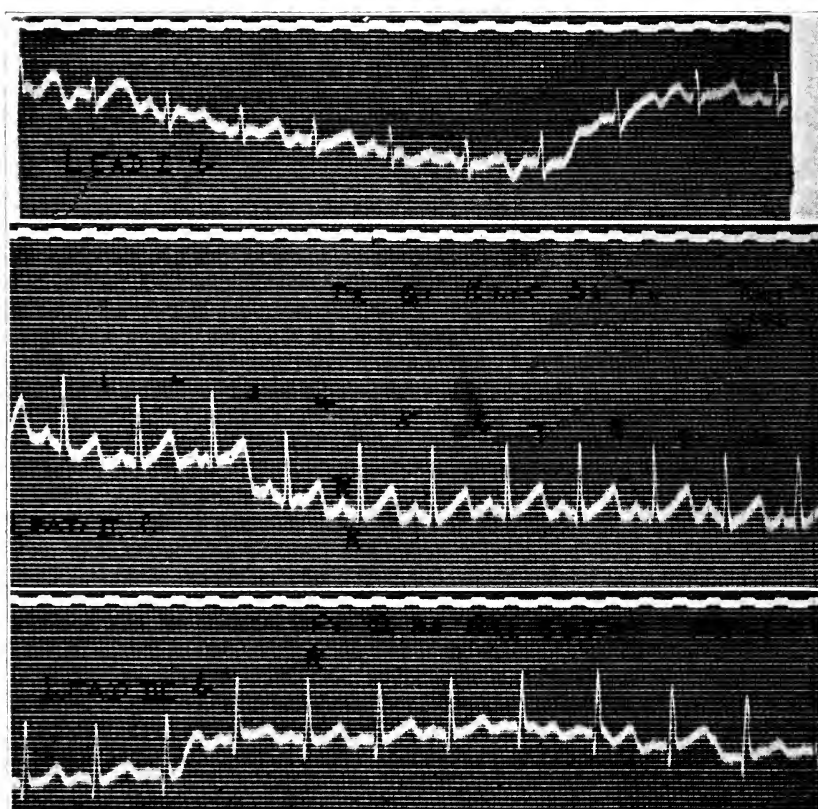
Fig. 19.—Electrocardiogram of the same new-born (Fig. 18) 6 months old.

sections of hearts of children of all ages shows that there is a definite right ventricular preponderance in the new-born and during the first two to three months; that, whereas in the adult the left ventricle weighs from 1.8 (Lewis) to 2.6 (Pfaundler) as much as the right ventricle, in the new-born the two ventricles are about equal. At birth the walls of the right ventricle are of about the same thickness as those of the left ventricle, slightly less. In other words, the L/R index of the thickness of the walls is from 0.66 to 1.0, and the L/R index of the weight is approximately 1.0.

Taking the adult electrocardiogram as a standard for comparison, it can be seen why that of the new-born shows a right ventricular preponderance, curve S 1 and 2. In this curve, the S is exaggerated in Lead I and shorter in Lead III. The R has very little or no amplitude in Lead I and is highest in Lead III. The Q is higher at this age in Lead II and III than in the adult. It should be mentioned, however, that the above anatomic figures are not entirely criticism proof; first, because there is insufficient material; secondly, because the measurements have been taken at different heights by different authors, and thirdly, because some of the cases reported are probably still-births, which fact presupposes disease or prematurity.

CONCLUSIONS

1. In the premature and during the first three months of life, the normal electrocardiogram indicates a right ventricular preponderance. At about the fourth month, the R_1 becomes larger than the S_1, and from then on the ventricular complex approaches the adult type of curve.

2. In general, the average heights of the deflections in childhood are greater than in the adult.

3. Except in the premature, satisfactory records showing all the deflections seen in the normal adult electrocardiogram can be obtained during any period of childhood.

4. The P is higher in childhood than in the adult, in all three leads. Except in the premature, it was absent in my series of cases in only two instances. It was found electronegative in eight records.

5. The Q plays a prominent part in the electrocardiogram of childhood. It is larger than in the adult, especially in Leads II and III. Altogether it adds confirmatory evidence that there is a right ventricular preponderance in the first few months of life.

6. The R in Lead I during the first few months of life is lower than at any other period, but in Leads II and III it averages higher than in the adult. The increase of R_1 corresponding with the decrease of S in Lead I is also indicative of a right ventricular preponderance during the earliest periods of life.

7. The S deflection is the most characteristic and distinctive of the ventricular complex in childhood. In Lead I it is both relatively and absolutely higher in the first three months than in any other period of life and in the other leads it is relatively higher than in the adult.

8. The T is very susceptible to external influences in the child, and therefore its height is unreliable. In the first ten days of life it is quite frequently absent. After that it is quite constant. It was found inverted, but only during the latter part of childhood, in 15 per cent. of the readings.

9. The general impression that the younger the child the more frequent the arrhythmias was not confirmed by the electrocardiograph. The younger the child, the faster the pulse; and the faster the pulse the less frequent the arrhythmias. In the new-born the average difference between the highest and lowest pulse periods was $\frac{2}{50}$ second, whereas in the older children (from 6 to 13 years) the average difference was $4\frac{3}{50}$ seconds. In the period of infancy, no sinus arrhythmia occurred (difference of 0.1 second or more) while in the school age 47 per cent. showed sinus arrhythmias.

10. The transmission time in children is, on the whole, of shorter duration than in the adult. In the new-born the auricular activity occupies an average of 0.113 second, whereas, in the last period of childhood it consumes an average of 0.138 second. In the adult the P R interval averages 0.18 second.

11. The ventricular conduction time in the child corresponds to the auricular. In the new-born it averages 0.21 second and gradually increases until at the school age it averages 0.34 second. In the adult the average for the R T period is 0.36 second.

12. The right ventricular preponderance which characterizes the first few months of life can best be explained by the relationship of muscle mass between the right and left ventricles.[14]

BIBLIOGRAPHY

14. The following references may also be found of interest.

Barker: Electrocardiography and Phonocardiography, Johns Hopkins Bull. **21**:359, 1913.

Einthoven, W.: Weiteres über das Elektrokardiogramm, Arch. f. d. ges. Physiol. **122**:517, 1908.

Einthoven, W.: Observations of the Movements of the Heart by Means of the Electrocardiogram, Proc. Roy. Soc. Med. (Clin. Sec.) **5**:183, 1911.

Eyster, T. A. F.: The Interpretation of the Normal Electrocardiogram; a Critical and Experimental Study, Arch. Int. Med. **11**:204 (Feb.) 1911.

Foa, S.: Electrocardiogram fetale, Gior. d. r. Accad. di. med. di Torino, **17**:90, 1911.

Fraser, F. R.: Changes in the Electrocardiogram Accompanying Experimental Changes in Rabbit's Heart, J. Exper. M. **22**:293, 1915.

Hering: Zur Erklärung des Elektrokardiogramm und seine klinische Verwertung, Deutsch. med. Wchnschr. **38**:2155, 1912.

James, W. B., and Williams, H. B.: The Electrocardiogram in Clinical Medicine, Am. J. M. Sc. **140**:1910.

Jolly, W. A.: On the Electrocardiogram, Quart. J. Exper. Physiol., Lond., **9**:43, 1915.

Kahn, R. H.: Weitere Beitraege zur Kenntnis des Elektrokardiogramms, Arch. f. d. ges. Physiol. **129**:291.

Kraus and Nicolai: Des Elektrokardiogram des gesunden und kranken Menschen. Leipsig, 1910.

Lewis, T: The Analysis of the Mammalian Levogram, J. Physiol. **49**: 26, 1915.

Lewis, T.: The Electrocardiographic Method and Its Relationship to Clinical Medicine, Proc. Roy. Soc. Med., Med. Sect. **4**:81, 1910.

Lewis, T.: A First Step in the Analysis of the Dog's Ventricular Electrocardiogram, Proc. Physiol. Soc. **20**:1915.

Lewis, T., and Allen, H. W.: An Instance of Premature Beats Arising in the Auricular Ventricular Bundle of a Young Child, Am. J. M. Sc. **145**:667, 1913.

Noeggerath: Das Elektrokardiogramm schwaechlicher Säuglinge (Fruehgeburten, Naehrschaeden und Infektionen), Ztschr. f. Kinderh. **6**:396, 1913.

Pardee, H. E. B.: Form of the Electrocardiogram. Diagnostic Significance of its Variations, J. A. M. A., **62**:1311 (April 25) 1914.

Pardee, H. E. B.: Electrocardiography as an Aid in the Diagnosis of Cardiac Valvular Diseases, Med. Rec. **91**:567, 1917.

Robinson, J.: Studies with the Electrocardiograph: I. The Action of the Vagus Nerve on the Human Heart. II. The Effect of Vagus Stimulation on the Hearts of Children with Chronic Valvular Disease, J. Exp. Med. **15**:14, 1912.

Rothberger, J. and Winterberg, H.: Ueber das Elektrokardiogramm bei Flimmern der Vorhoefe, Arch. f. d. ges. Physiol. **13**:387, 1910.

Talley, J. E.: The Electrocardiograph as a Clinical Instrument, Tr. Coll. Phys. Phila. **35**:317, 1913.

Visco, F.: Arythmien im Kindesalter, Monatschr. f. Kinderh. **10**:262, 1911.

Voegelmann, S.: Der Einfluss des Lebensalters auf die Relative Groesse der J. und Jp. Zacke, Ztschr. f. exper. Path. u. Therap. **17**:11, 1914.

Waller, A. D.: A Short Account of the Origin and Scope of Electrocardiography, Harvey Lect. **9**:17, 1915.

Wells: Clinical Electrocardiography, Practitioner, London **96**:347, 1916.

Williams: On the Cause of the Phase Difference Frequently Observed Between Homonymous Peaks of the Electrocardiogram, Am. J. Physiol. **35**:292, 1914.

PHYSICAL DEFECTS IN CHILDREN

REPORT OF SIX HUNDRED AND TWO CASES *

WILLIAM R. P. EMERSON, M.D.

Professor of Pediatrics, Tufts College Medical School

BOSTON

In an article published in 1917,[1] a group study was presented show-ing the results of one hundred physical and mental examinations of so-called well children made at the Little Wanderers' Home in Boston. This report includes the children in the former study, together with 145 additional examinations made at the same institution, and 357 made in the Children's Out-Patient Department of the Massachusetts Gen-eral Hospital.

One of the objects of the investigation has been to emphasize the importance of more systematic and thorough methods of physical exam-ination for all children. A standard form has been worked out in our nutrition clinics,[2] which covers all the practical points in examina-tion in regular order; second, enables different examiners to cover the same ground; third, saves clerical work by so arranging descriptive matter as to allow underlining instead of writing; fourth, acts as a check on the work of the examiner, since a failure to underline an item shows failure to examine.

I. DEFECTS FOUND

The children examined in the Little Wanderers' Home exhibited a larger proportion of defects than would be found in an ordinary school, yet each of these children had already been given a routine examination and declared to be sufficiently well to attend school and to engage in the ordinary activities of normal children. The other and larger group is made up of the usual type of child met in the out-patient department of a large hospital.

The advantages of more adequate examinations of children in both these classes are evident. In the hospital, there is great waste of time and energy due to the result of failure to make complete initial exam-inations and records. The value to those concerned with members of "the so-called well" group appears in the case of O. B., a boy aged 7,

---

1. A group study of the results of one hundred physical and mental exam-inations of so-called well children. Internat. Clin. **2**: Series 27, 1917.

2. A copy of this form for history and physical examination, with other blanks and forms used in our nutrition clinics, will be found in an article on malnutrition in children, a class clinic, in Internat. Clin. **4**: Series 29, 1919.

who, after having been reported normal, was found to require care for ten defects: (1) 15 per cent. underweight for height; (2) adenoids; (3) hypertrophic pharyngitis; (4) diseased tonsils; (5) five carious teeth; (6) enlarged cervical glands; (7) cerumen in both ears; (8) round shoulders; (9) adherent prepuce; (10) mouth breathing. This was one of the worst cases found, yet Table 1 shows that twelve children, or 5 per cent. of the group to which this boy belonged, had ten or more defects. The distribution of defects in this group, according to number, is shown in Table 1.

TABLE 1.—Number of Defects Per Individual Among Six Hundred and Two Examined

Number of Defects	Little Wanderers' Home, 245 Cases	Massachusetts General Hospital, 357 Cases
None	4	5
One	8	2
Two	24	5
Three	34	12
Four	36	26
Five	33	32
Six	32	54
Seven	31	78
Eight	24	85
Nine	7	35
Ten	9	12
Eleven	2	7
Twelve	1	4

It will be noted that the mode—the largest number of cases—is the group of four defects in the Little Wanderers' Home class and that of eight in the Massachusetts General Hospital class. The average number of defects found in the former was 5.2, and in the latter, 6.8. The larger number resulting from the Massachusetts General Hospital examinations is due, in great part, to two causes: first, as stated above, these latter children were candidates for clinic care, and so, elite, represented a lower grade of physical condition; second, these examinations were conducted later than those in the Little Wanderers' Home class when our method of examination and record had been so worked out that fewer defects escaped observation.

The children represented all stages of the school and preschool periods, but the largest number in each institution were from 7 to 9 years of age. Table 2 shows that at least a majority of physical defects were present as early as the preschool period.

Table 2 shows a remarkable uniformity in defects at various ages. There is no evidence of any particular age at which children have an especially large number of defects.

Because we have found obstruction to breathing to be a serious matter as regards growth and development, we have made a special

grouping of nasopharyngeal defects. Here, again, we find remarkable uniformity at various ages.

TABLE 2.—AVERAGE NUMBER OF PHYSICAL DEFECTS AT VARIOUS AGES

Age	Little Wanderers' Home			Massachusetts General Hospital		
	Per Cent. of Total Group	Average Number Defects		Per Cent. of Total Group	Average Number Defects	
		All Kinds	Naso-pharyngeal		All Kinds	Naso-pharyngeal
3 and under.......	12	5.0	3.9	9	6.0	3.6
4–6.................	21	5.0	2.5	23	6.9	3.5
7–9.................	23	5.1	2.3	30	7.2	3.6
10–12...............	18	6.0	3.3	28	6.9	3.8
13 and over........	17	4.3	2.4	6	6.0	3.0
Unknown..........	9	3.5	1.3	4	6.4	3.5
Entire group......	100	5.2	2.5	100	6.8	3.5

Table 3 gives a summary of the most general facts brought out in the examinations. These are grouped in order to show, first, the number of individual cases found suffering from certain defects; and, second, the actual number of defects found. For convenience the results are stated in the four classes which it has seemed most important to distinguish in order to study their incidence—underweight, nasopharyngeal obstruction, carious teeth, and defects of posture.

TABLE 3.—SUMMARY SHOWING NUMBER OF INDIVIDUALS HAVING DEFECTS AND NUMBER OF DEFECTS

Cases Suffering from Defects	Little Wanderers' Home						Massachusetts General Hospital					
	Male		Female		Both Sexes		Male		Female		Both Sexes	
	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.	Cases	Per Cent.
Number of physical examinations made..	160	100	85	100	245	100	163	100	194	100	357	100
Number found not needing treatment...	2	...	2	...	4	...	3	...	2	...	5	...
Cases of nasopharyngeal obstruction.....	140	88	73	86	213	87	159	98	185	95	344	96
Cases of teeth defects.	95	59	48	56	143	58	115	71	138	71	253	71
Cases of postural defects.................	83	52	38	45	121	50	109	67	142	73	251	70
Actual Number of Defects Found	De-fects	Per Cent.	De-fects	Per Cent.	De-fects	Per Cent.	De-fects	Per Cent.	De-fects	Per Cent.	De-fects	Per Cent.
Underweight for Ht.* 10% and over........	43	27	23	27	66	27	95	58	127	66	222	62
7% and over........	...	...	...	...	...	...	118	72	150	77	268	75
Nasopharyngeal.......	393	246	224	263	617	252	593	364	656	338	1249	350
Teeth.................	114	71	50	59	164	67	129	79	147	76	276	78
Postural..............	118	74	56	66	174	71	145	89	201	106	346	97
Other................	146	91	96	113	242	100	141	86	143	74	284	80
Total basis 10% underweight..............	814	509	449	528	1263	517	1103	676	1274	660	2377	667
Total basis 7% underweight.............	....	....	....	....	....	....	1126	690	1297	671	2423	680
Number of cases with mental defects.......	58	36	23	27	81	33						

* In underweight for height the number of cases and the number of defects is, of course, the same.

Table 4 presents the remaining defects found. These are not used in the incidence tables, but should be useful in making comparisons with the results of other examinations.

In Table 5 will be found a comparison between the results we have secured in the two institutions and those which appear in examinations made in the course of school medical inspection in two of our largest cities.

TABLE 4.—Summary of "Other" Defects Not Presented in Incidence Tables

	Little Wanderers' Home			Massachusetts General Hospital		
	Male	Female	Both	Male	Female	Both
Eyes...........................	7	4	11	5	8	13
Ears:						
Cerumen and foreign bodies...	41	25	66	25	36	61
Otitis media*..................	14	13	27	7	6	13
Thickened drum*..............	0	0	0	87	82	169
	—55	—38	—93	—119	—124	—243
Cardiac.........................	2	1	3	2	6	8
Lungs..........................	3	4	7	8	4	12
Skin...........................	13	15	28	13	21	34
Genito-urinary system...........	57	7	64	41	5	46
Enuresis.......................	9	10	19	11	8	19
Pediculosis.....................	10	22	32	19	43	62
Nervous system.................	1	1	2	5	1	6
Overweight.....................	0	1	1	1	10	11
Anemia........................	2	1	3	1	0	1
Cleft palate....................	0	0	0	1	0	1
Periosteitis....................	1	5	6	0	0	0
Tuberculosis...................	0	0	0	6	1	7
Infantile paralysis..............	0	0	0	1	0	1
Measles.......................	0	0	0	1	0	1
Pertussis......................	0	0	0	1	0	1

* Otitis media and thickened drum are also included in nasopharyngeal defects.

TABLE 5.—Comparison Between the Results Presented in This Study and Those Found in Two Representative City School Medical Inspections

Defects	Little Wanderers' Home, per Cent.	Massachusetts General Hospital, per Cent.	1919 New York, per Cent.	1918 Philadelphia, per Cent.
Number examined..................	245	357	248,978	147,631
Vision.............................	4.5	3.6	7.2	13.5
Hearing...........................	38.0	69.0	0.5	9.8
Nasopharyngeal....................	252.0	350.0	26.8	16.2
Defective nutrition.................	27.0	75.0	20.0	11.7
Cardiac...........................	1.2	2.2	1.6	0.6
Pulmonary........................	2.8	3.4	0.3	
Orthopedic........................	64.0	96.0	0.9	15.5
Nervous system....................	0.8	2.0	0.6	0.3
Teeth.............................	67.0	77.0	62.0	48.0
Skin..............................	11.5	9.5	....	6.5
Pediculosis........................	13.0	17.5	....	4.1
Enuresis..........................	7.7	5.3	....	0.015
Genito-urinary system..............	26.0	13.0		
Stoop shoulders....................	42.0	65.0	....	1.3
Lateral curvature..................	15.0	22.0	....	0.13
Flat foot..........................	6.0	9.0	....	0.006

Comparison with Results of Other Studies.—Little attempt has been made to compare the results secured in these examinations with those coming from any other studies. The difficulties in the way of such

comparisons are due, principally, to two causes: first, the difference in attitude and approach of various physicians making the examinations; second, the varying physical conditions found among different groups of children.

The first of these will be remedied as fast as it is possible to standardize examinations along uniform lines. The second difficulty is similar to that found in various studies made with reference to the apparent increase of certain diseases among adults. Changes in type of population and other factors must be carefully investigated before generalizations can be made. This wide variation is illustrated in a study made in New York City of about 2,500 school children. It was found that these children showed an average of 49 per cent. of teeth defects and 61 per cent. of tonsil defects. But an analysis of these figures showed that in teeth defects the boys averaged 45 per cent. and the girls 53 per cent.; in tonsil defects the boys averaged 54 per cent. and the girls 70 per cent. A further analysis among the boys showed that the percentage in teeth defects for the foreign born was 36, for the native born, 48; in tonsil defects the foreign born averaged 46 per cent. and the native born 52 per cent.

When the various nationalities were separated, generalization became even more difficult, as shown in Table 6.

TABLE 6.—THE DISTRIBUTION OF TEETH AND TONSIL DEFECTS
ACCORDING TO NATIONALITY *

	United States, per Cent.	Italy		Russia, Poland		Germany, Austria		Hebrew	
		Foreign Born, per Cent.	Native Born, per Cent.	Foreign Born, per Cent.	Native Born, per Cent.	Foreign Born, per Cent.	Native Born, per Cent.	Foreign Born, per Cent.	Native Born, per Cent.
Teeth..	52	37	43	59	40	24	48	30	56
Tonsils	50	49	55	63	39	37	53	42	54

* A New York City study made by the Association for Improving the Condition of the Poor.

Number of Defects Found by Different Examiners.—The differences in the defects found in examinations made by various physicians were studied at the same time. Two hundred and sixty-six children were examined consecutively but independently by each of three physicians who were found to agree in only 75 per cent. of the cases with reference to the presence or absence of carious teeth, and in 63 per cent. with reference to the presence or absence of diseased tonsils.

Relationship of School and Growth Records to Defects.—In this New York study, a further comparison was made of the correlation found between teeth and tonsil defects, on the one hand, and, on the other, school attendance and promotions, also height and weight.

School attendance was based on the actual records for an entire year. Promotions were studied with reference to the changes made in school grade by each child during the same period of time. Height and weight were based on the relationship of each child to the Boas-Burk averages for his age.

The first line in Table 7, under boys, would be read: "Boys having no teeth defects showed over those having such defects 7 per cent. better attendance in school, made 6 per cent. more promotions, showed no difference in height for their age, and 7 per cent. more weight for their age."

TABLE 7.—STUDY OF 1,242 SCHOOLCHILDREN WITH REFERENCE TO THE RELATION OF TEETH AND TONSIL DEFECTS TO SCHOOL ATTENDANCE, PROMOTION, HEIGHT AND WEIGHT (A. I. C. P., NEW YORK)

	School Attendance, per Cent.	School Promotions, per Cent.	Height, per Cent.	Weight, per Cent.
Boys:				
No teeth defects..................	7	6	0	7
No tonsil defects.................	7	1	6	7
Neither teeth nor tonsil defects...	10	8	5	8
Girls:				
No teeth defects..................	..	3	4	15
No tonsil defects.................	..	3	6	14
Neither teeth nor tonsil defects...	..	15	14	25

TABLE 8.—COMPARISON OF THE RESULTS OF THE EXAMINATION OF FIFTY CHILDREN * (BOTH SEXES) AT A CHILDREN'S CLINIC AND AT THE NUTRITION CLINIC

Defects Found	(1) Defects Appearing in Diagnosis Summary	(2) Additional Defects Shown in Various Parts of Record	(3) Total of (1) and (2)	(4) Defects Found in Nutrition Clinic	(5) Per Cent. (3) of (4)	(6) Per Cent. (1) of (4)
Cases exam. ...	50	50	50	50	100	100
All defects:						
Cases........	42	38	50	50		
Defects......	83	93	176	401	44	20.8
Nasopharyn- geal:						
Cases........	12	28	32	50	30	8.9
Defects......	17	40	57	191		
Teeth:						
Cases........	15	17	32	32	100	47
Defects......	..	..	..	150		
Postural:						
Cases........	10	8	18	50		
Defects......	11	9	20	108	18.5	10.2
Underweight:						
Cases........	11	21	32	39	82	28

* Average age about 9 years.

Table 8 presents some very interesting data showing the defects found in fifty children who were patients in one of our largest and best organized children's clinics, as compared with the results of the

examinations of the same children made in our nutrition clinic. The figures are given in four columns, showing, first, the defects appearing in the diagnosis summary; second, the additional facts scattered through the cards filed in the case; third, the total of (1) and (2); and, fourth, the defects found in the examination made at the nutrition clinic. The fifth and sixth columns show the percentage comparisons. The general examination found only 44 per cent. of the number of defects appearing in the records of the examination at our nutrition clinic, and in the various groups, from 18.5 per cent. in defects of posture to 100 per cent. in teeth defects.

It would be more reasonable (column 6) to compare the summary of defects made in the nutrition clinic examinations with the first column giving the summary in the other situation. This greatly decreases the percentages shown in the fifth column, for only 20.8 per cent. of all defects found in the nutrition examination appear in the diagnosis summary, ranging from 8.9 per cent. of nasopharyngeal obstructions to 47 per cent. of teeth defects. If the results of an examination are not clearly stated in the diagnosis summary, they are usually overlooked, as treatment is rarely ordered except for defects thus stated.

It might be urged that the general examination is especially concerned with the vital organs, and omits only the less essential defects, but an inspection of the results of the more complete examination shows that no defects have been included which do not have direct bearing on the health of the child.

II. INCIDENCE OF DEFECTS

The larger groups in this study have been analyzed in order to find the correlation of defects. These groups include underweight, nasopharyngeal obstructions, teeth defects, and postural defects. In the last named group, further analysis has been made of round shoulders, lateral curvature and flat foot.

The comparisons in each section are between those individuals showing the particular defect and those who were free from it, as well as with the total group including both.

Nasopharyngeal Obstruction.—Table 9 shows the various nasopharyngeal obstructions found as well as their distribution in the children from the two institutions studied:

In Table 10 is indicated the percentage of postural, underweight and teeth defects occurring in the nasopharyngeal group, as compared with those who were free from these obstructions, as well as with the

entire membership in both sections of the study. It will be recalled that only 13 per cent. of those examined at the Little Wanderers' Home, and 4 per cent. of those at the Massachusetts General Hospital, were found to be free from nasopharyngeal defects.

TABLE 9.—Distribution of Nasopharyngeal Obstruction

Defects	Little Wanderers' Home			Massachusets General Hospital		
	Male, per Cent.	Female, per Cent.	Both, per Cent.	Male, per Cent.	Female, per Cent.	Both, per Cent.
Adenoids	62	65	63	29	21	25
Hypertrophic pharyngitis	42	46	44	77	78	77
Diseased tonsils	50	55	52	67	60	63
Deviated septum	15	12	14	10	5	7.5
Spur	5	2.4	4	2.5	1.5	2
Hypertrophic turbinates	17	20	17.5	1	3	2.2
Open mouth	18.5	30	23	59	59	59
Enlarged anterior cervical glands	26	20	24	61	65	63
Otitis media	9	15	11	4	3	3.6
Thickened drum	0	0	0	53	42	47
Total	244.5	265.4	252.5	363.5	337.5	349.3

TABLE 10.—Incidence of Postural, Teeth, and Underweight Defects in the Nasopharyngeal Group

Defects	Nasopharyngeal Defect								
	Male			Female			Both Sexes		
	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.
Little Wanderers' Home									
Postural	54	38	52	47	31	44	52	35	49
Teeth	59	66	59	60	33	56	59	53	58
Underweight	26	29	26	26	31	27	26	29	26
Mass. General Hospital									
Postural	67	67	67	74	50	73	71	54	70
Teeth	71	33	71	74	30	71	73	31	71
Underweight	73	67	73	77	70	77	75	69	75

The comparison shows that among the girls, those having nasopharyngeal defects indicate for the Little Wanderers' Home and Massachusetts General Hospital sections 16 and 24 per cent., respectively, more postural defects than occur among those free from these obstructions. A like disadvantage in this respect appears among the boys of the former institution. In like manner, three out of four sex divisions show from 27 to 44 per cent. more teeth defects than appear in the cases free from nasopharyngeal obstruction. In percentage of defects from underweight for height, the Little Wanderers' Home children show a negative correlation, but those in the Massachusetts General Hospital section show a positive relation of 6 and 7 per cent.

Defects of the Teeth.—The lack of correlation between malnutrition and carious teeth is remarkable. There seems to be no evidence that small cavities in teeth affect nutrition unless there are also abscesses or other inflammatory conditions. Below are given the distribution of cases and of defects.

TABLE 11.—Distribution of Defects of Teeth

Defects	Little Wanderers' Home			Massachusetts General Hospital		
	Male Cases	Female Cases	Both Sexes Cases	Male Cases	Female Cases	Both Sexes Cases
Carious teeth........	89	47	136	118	138	256
Approximation......	6	1	7	2	0	2
Alveolar abscess.....	5	0	5	5	4	9
Gingivitis...........	1	1	2	1	0	1
Pyorrhea...........	0	0	0	0	1	1
Stomatitis..........	0	1	1	0	1	1
Total cases........	95	48	143	118	138	256
Per cent.	59	56	58	72	71	72
Total defects......	101	50	151	126	144	270
Per Cent.	63	59	62	77	75	76

In Table 12 the most evident correlations are found between teeth and postural defects, ranging from 7 to 22 per cent. of the latter among children suffering from the former. Three of the four divisions on the basis of sex show from 4 to 16 per cent. greater incidence of naso-pharyngeal obstruction among those having teeth defects. Only one of the four divisions shows a positive correlation between teeth defects and underweight.

TABLE 12.—Incidence of Nasopharyngeal, Postural, and Underweight Defects with Reference to Defects of the Teeth

Defects	Teeth Defects								
	Male			Female			Both Sexes		
	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.
Little Wanderers' Home									
Nasopharyngeal.......	85	86	86	92	76	85	87	83	85
Postural..............	57	44	54	54	32	44	56	39	49
Underweight..........	24	29	26	23	32	27	24	30	26
Mass. General Hospital									
Nasopharyngeal.......	100	96	98	97	89	95	98	92	96
Postural..............	72	55	67	79	62	73	75	60	70
Underweight..........	72	75	73	78	73	77	76	74	75

Defects of Posture.—Comparing the results of the examinations forming the basis of this study with those made in large numbers in New York and Philadelphia indicates that much remains to be accomplished in working out and using more effective methods of diagnosis

of postural defects. In the latter city fewer cases of flat foot, for instance, were recorded as a result of nearly 150,000 examinations than are here found in 100.

TABLE 13.—DISTRIBUTION OF POSTURAL DEFECTS

Defects	Little Wanderers' Home			Massachusetts General Hospital		
	Male, per Cent.	Female, per Cent.	Both Sexes, per Cent.	Male, per Cent.	Female, per Cent.	Both Sexes, per Cent.
Lateral curvature...	15	15	15	13.5	28	22
Round shoulders.....	43	39	42	66	65	65
Flat foot............	9	0	6	8.5	9	9
Bow legs............	0	0	0	0	1	0.5
Rickets.............	7	8.5	6.8	1	0	0.5
Enteroptosis........	0	3.5	1.2	0	0	0
Defects..........	74	66	71	89	103	97
Cases...........	52	45	50	67	73	70

The incidence of other defects among cases having postural defects shows a positive correlation in every sex division but one. The excess runs from 10 to 23 per cent. among the members of the Little Wanderers' Home section, and from 16 to 23 per cent. in the Massachusetts General Hospital figures. In three out of four divisions the nasopharyngeal obstructions show 9 and 10 per cent. greater incidence, and underweight appears more definitely than it does in the other correlations studied, amounting to 16 and 4 per cent. among boys and girls of the Little Wanderers' Home section, and 4 and 23 per cent. among the others.

TABLE 14.—INCIDENCE OF NASOPHARYNGEAL, TEETH AND UNDERWEIGHT
DEFECTS IN POSTURAL DEFECT GROUP

Defects	Postural Defects								
	Male			Female			Both Sexes		
	Cases Showing, per Cent.	Cases Not Showing, per Cent.	Total Cases, per Cent.	Cases Showing, per Cent.	Cases Not Showing, per Cent.	Total Cases, per Cent.	Cases Showing, per Cent.	Cases Not Showing, per Cent.	Total Cases, per Cent.
Little Wanderers' Home									
Nasopharyngeal.......	91	81	86	90	81	85	90	81	85
Teeth.................	64	54	59	69	46	56	65	51	58
Underweight..........	34	18	26	29	25	27	32	21	27
Mass. General Hospital									
Nasopharyngeal.......	98	98	98	97	88	95	98	98	96
Teeth.................	76	60	71	75	62	71	75	61	71
Underweight..........	74	70	73	83	60	77	79	65	75

In the tables dealing with the various forms of postural defect, those for flat foot and lateral curvature show each a correlation with round shoulders. The former also shows a greater incidence of lateral curvature, while lateral curvature indicates in three out of the four sex divisions a greater frequency of teeth defects.

When we turn to the figures on round shoulders, we find positive correlations in all but one of the sixteen divisions. This is most marked in relation to "other postural defects"; second, in relation to teeth; third, to underweight, and least, to nasopharyngeal obstruction.

TABLE 15. — INCIDENCE OF VARIOUS OTHER DEFECTS IN ROUND SHOULDERS, LATERAL CURVATURE, AND FLAT FOOT SUBGROUPS

Defects	Male			Female			Both Sexes		
	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ir g, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.
Round Shoulders									
Little Wanderers' Home									
Other postural.........	31	15	22	39	10	21	33	13	21
Nasopharyngeal.......	91	84	87	88	83	85	90	83	86
Teeth.................	66	53	59	70	47	56	67	51	58
Underweight..........	35	20	26	30	25	27	33	21	26
Mass. General Hospital									
Other postural.........	30	9	22	39	10	21	33	13	21
Nasopharyngeal.......	98	98	98	88	83	85	90	83	86
Teeth.................	80	64	75	70	47	56	67	51	58
Underweight..........	77	66	73	85	60	77	81	63	75
Lateral Curvature									
Little Wanderers' Home									
Round shoulders.......	63	13	22	83	30	38	70	19	27
Nasopharyngeal.......	97	85	87	75	87	75	90	85	87
Teeth.................	52	60	59	83	51	56	62	57	59
Underweight..........	26	26	26	58	22	27	36	24	26
Mass. General Hospital									
Round shoulders.......	85	47	53	87	59	68	80	53	61
Nasopharyngeal.......	100	98	98	100	92	95	100	95	97
Teeth.................	77	70	71	75	70	71	75	70	71
Underweight..........	69	73	72	77	77	77	75	76	75
Flat Foot									
Little Wanderers' Home									
Round shoulders.......	57	41	43	..	..	..	..	..	..
Lateral curvature.....	35	15	17	..	..	..	..	..	..
Teeth.................	50	60	59	..	..	..	..	..	..
Nasopharyngeal.......	93	87	87	..	..	..	..	..	..
Underweight..........	28	26	26	..	..	..	..	..	..
Mass. General Hospital									
Round shoulders.......	85	62	64	24	66	62	50	65	63
Lateral curvature.....	23	15	15	48	29	31	37	23	24
Teeth.................	54	72	93	95	70	71	77	71	71
Nasopharyngeal.......	92	99	98	95	95	95	94	97	97
Underweight..........	61	74	73	71	78	77	67	76	75

Underweight Group.—The incidence of other defects among those falling from 7 to 10 per cent. underweight for their height is most marked in the case of round shoulders and the general posture group. This is shown in Table 16.

From this table it is evident that the incidence of persons suffering from nasopharyngeal obstruction is not marked among those who are underweight, but a study of the actual number of defects of this type shows a greater correlation in this respect as well as in the average number of defects of all kinds for each individual. In both instances, the correlation is positive in all four divisions.

When, however, account is taken of the actual number of carious teeth reported, the incidence is reversed. These relationships are shown in Table 17.

TABLE 16.—INCIDENCE OF NASOPHARYNGEAL, TEETH, POSTURAL, ROUND SHOULDERS, LATERAL CURVATURE AND FLAT FOOT DEFECTS IN UNDERWEIGHT GROUP

	Underweight								
	Male			Female			Both Sexes		
Defects	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.	Cases Show-ing, per Cent.	Cases Not Show-ing, per Cent.	Total Cases, per Cent.
Little Wanderers' Home									
Nasopharyngeal.......	86	87	87	83	86	85	85	87	86
Teeth.................	55	60	59	48	60	56	52	60	58
Postural..............	67	46	52	48	43	44	60	45	49
Round shoulders.......	56	38	43	44	37	38	52	37	41
Lateral curvature.....	17	17	17	30	80	14	22	14	16
Flat foot.............	10	8	9	..	..	..	..	..	..
Mass. General Hospital									
Nasopharyngeal.......	98	98	98	95	95	95	96	97	97
Teeth.................	70	73	71	72	67	71	72	70	71
Postural..............	69	64	67	79	53	73	75	60	71
Round shoulders.......	68	55	64	75	45	68	72	50	66
Lateral curvature.....	15	18	16	31	31	31	24	25	24
Flat foot.............	7	11	8	8	11	9	8	11	9

TABLE 17.—INCIDENCE OF TOTAL NUMBER OF DEFECTS OF ALL KINDS, ALSO NASOPHARYNGEAL AND TEETH DEFECTS IN UNDERWEIGHT GROUP

	Little Wanderers' Home				Massachusetts General Hospital			
	Male		Female		Male		Female	
	Underweight		Underweight		Underweight		Underweight	
	Cases Show-ing	Cases Not Showing	Cases Show-ing	Cases Not Showing	Cases Show-ing	Cases Not Showing	Cases Show-ing	Cases Not Showing
Average number of all physical defects..............	5.6	5.1	6.2	5.0	6.9	6.5	6.7	6.2
Average number of nasopharyngeal defects...........	2.7	2.6	3.3	3.0	3.8	3.4	3.4	3.3
Average number of carious teeth......	3.3	4.0	4.7	4.0	4.1	4.4	3.6	4.0

III. RELATION TO MENTAL RETARDATION

At the Little Wanderers' Home mental examinations were also made.[3] Modified Binet-Simon and Yerkes-Bridges scales were used. The complete records of 155 cases have been placed in three groups: (1) those who received a grade of more than one year above normal expectation; (2) those less than a year above or below normal; (3) those a year or more below normal. The differences are not sufficiently large to make an evident case, but their general trend is suggestive.

3. By Rose S. Hardwick, A.M.

The correlation between degree of mental retardation and total number of physical defects, nasopharyngeal defects, and carious teeth is striking. On the other hand, the worst postural conditions appear to be in the superior mental group, and the worst conditions of underweight in the medium mental group.

TABLE 18.—Summary Showing Relative Incidence Between Various Groups and Subgroups

In making the following list the amounts of the total incidence, both positive and negative, in the four sex divisions have been taken as a rough index of the degree of incidence shown among the various groups studied. The pairs of terms are arranged in the order which the totals indicate.

    1. Lateral curvature and round shoulders
    2. Nasopharyngeal and teeth (see 12)
    3. Round shoulders and other postural defects
    4. Round shoulders and teeth
    5. Underweight and round shoulders (see 9a)
    6. Teeth and posture (see 7)
    7. Posture and teeth (see 6)
    8. Underweight and posture (see 10)
    9a. Round shoulders and underweight (see 5)
    9b. Nasopharyngeal and posture (see 13)
    10. Posture and underweight (see 8)
    11a. Lateral curvature and underweight
    11b. Lateral curvature and teeth
    12. Teeth and nasopharyngeal (see 2)
    13. Posture and nasopharyngeal (see 9b)

TABLE 19.—Incidence of Physical Defects of All Kinds, Also Nasopharyngeal Defects, in Three Mental Grades

	(1) 1 Year or More Above Scale	(2) Less than 1 Year Above or Below Scale	(3) 1 Year or More Below Scale
Average number of physical defects of all kinds	4.6	4.8	5.1
Average number of nasopharyngeal defects.....	1.9	2.2	2.4
Per cent. defects of all kinds......................	15	33	52
Per cent. nasopharyngeal defects.................	74	84	91
Per cent. teeth defects............................	39	57	63
Per cent. postural defects........................	61	47	55
Per cent. underweight	17	37	28

SUMMARY

The evidence presented points to the following general statements:

1. Children reported to be sufficiently well to attend school, and to engage in the ordinary activities of normal children, were found to average 5.2 physical defects of all kinds and 2.5 nasopharyngeal defects (Table 1).

2. Children brought to a hospital clinic for examination and treatment showed an average of 6.8 defects of all kinds and 3.5 nasopharyngeal defects (Table 1).

3. The distribution of number of defects according to age was remarkably uniform. In each group studied the largest number of children were between the ages of seven and nine. These years showed the greatest average number of defects in the Massachusetts General

Hospital group (7.2), but in the Little Wanderers' Home group the highest average number of defects (6.0) was found in the years from ten to twelve. There is no evidence of any particular age at which children have an especially large number of defects (Table 2).

4. Only nine children of the six hundred and two examined were found to be free from defects (Table 3).

5. The nasopharyngeal defects appeared in a larger number of cases (Little Wanderers' Home, 87 per cent., Massachusetts General Hospital, 96 per cent.), and also totaled a greater number of defects than any other group (Little Wanderers' Home, 49 per cent. of all defects found, Massachusetts General Hospital 53 per cent. of all) (Table 3).

6. The most striking differences in percentages of physical defects found in the comparison with results secured in public schools in New York and Philadelphia are in hearing, nasopharyngeal obstruction, malnutrition and posture (Table 5).

7. In one of our largest and best conducted children's clinics about half the defects found in the examinations were brought down in the summary for diagnosis purposes. The complete examination of the same children made in our nutrition clinic showed that the general examination had found only 44 per cent., and the diagnosis summary had recorded less than 21 per cent. of the defects revealed in the nutrition examination. The greatest discrepancies occurred in nasopharyngeal, postural and teeth defects, in the order named (Table 8).

8. The correlation between the total number of nasopharyngeal defects and those of underweight was much more clearly marked than that between the number of nasopharyngeal cases and underweight (Table 17).

9. The correlation between the actual number of carious teeth found and underweight was negative in three out of four of the sex groups (Table 17).

10. The summary of relative incidence indicates that postural defects, especially round shoulders, have greater value for diagnosis purposes in malnutrition than is usually assigned them (Table 18).

11. The mental tests made in the Little Wanderers' Home group showed positive correlation between mental retardation and the total number of all physical defects, nasopharyngeal, and teeth defects (Table 19).

THE INFANT OF LOW BIRTH WEIGHT; ITS GROWTH AND DEVELOPMENT *

HERMAN SCHWARZ, M.D., AND JEROME L. KOHN, M.D.

NEW YORK

The "impulse to grow" is being recognized as a very interesting and important phenomenon in the study of infancy and childhood. The growth in utero seems to be divided into two well defined parts; that of the first six months, and that of the last three months. Of the first period, not so much is known, for the opportunities to study this growth are relatively few. The second period, that of the last three months in utero, has been rendered very important from the pediatric point of view, firstly, because there is great growth during this period, and secondly, because this period is unfortunately often spent outside, instead of inside the uterus. It has always been an interesting theme to know whether:

(a) if the infant, although of full term, for some unknown reason does not obtain this added growth of the last three months and comes into the world very much underweight and underdeveloped, or,

(b) if the infant is born prematurely and thus fails to obtain this stimulus of the last few months, does it develop more rapidly than the normal (after being born), or, does it lag behind physically and mentally, and when, if ever, does it catch up to the normal?

It was in the endeavor to answer some of these questions that we have followed our cases. This opportunity was given us under the supervision of the John E. Berwind Maternity Clinic, a free outdoor maternity clinic. These children were delivered in their homes. Soon after birth a nurse with pediatric experience visited them, weighed and cared for them, repeated her visits daily for three days, then again visited them on the seventh and fourteenth days, urged breast feeding and instructed the mother. When 4 to 6 weeks old, the children were brought to the clinic and thereafter seen monthly or more often, if necessary, for one year or more.

We have had 272 children with low birth weights in 11,100 deliveries, an incidence of 25 per 1,000 pregnancies (2.5 per cent.). We have arbitrarily made 2,500 gm. or under, the weight designated as low birth weight.

Miller[1] collected 6,000 cases of low birth weight in 121,626 deliveries, an incidence of 5 per cent. Ylppo[2] had 114 cases in 2,168 deliveries, or 5 per cent. and Schmitt[3] had 316 cases in 8,516 deliveries, or 3.6 per cent. Holt and Babbitt[4] had 183 cases out of 9,160 deliveries with a birth weight under 5 pounds, or about 2 per cent. It would appear, therefore, that from 2 to 5 per cent. of all pregnancies result in infants (a) that have either been born prematurely, (b) are one of twins and have had their growth retarded at the expense of the other twin, or (c) a full term infant of low birth weight.

The material as shown in Table 1 consisted of 163 cases from single pregnancies, and 109 from twin pregnancies. The twin pregnancies at times represent both children from the one mother; at other times, one twin, the other being an infant with a normal weight. The infants were deemed premature, first by means of the history, as far as possible, and by weight, length and other clinical signs.

Of the 272 infants, three were under 1,000 gm. weight, sixteen were between 1,000 and 1,500 gm., forty-nine were between 1,500 and 2,000 gm. and 204 were between 2,000 and 2,400 gm. weight.

TABLE 1.—Analysis of Cases

272 live born children; 163 single pregnancies; 109 twin pregnancies

	Number Under 1,000 Gm.	No. from 1,000 to 1,500 Gm.	No. from 1,500 to 2,000 Gm.	No. from 2,000 to 2,400 Gm.	Total
Single pregnancies.......	1	7	21	134	163
Twin pregnancies.......	2	9	28	70	109
Total number........	3	16	49	204	272

Of these cases, 166 were followed for three months, 130 for six months, 100 for twelve months and twenty-six a greater length of time. We lost by death and otherwise almost one-half of the cases before the end of the first three months.

MORTALITY

It is difficult to obtain the mortality rate of these children with any degree of accuracy because of the inabilty to keep track of this class of population over long periods of time. It seemed more advisable to

1. Miller, N. Th.: Jahrb. f. Kinderheilk. **25**:179, 1886.
2. Ylppo, A.: Ztschr. f. Kinderheilk. **24**:1, 1919.
3. Schmitt, H.: Ztschr. f. Geburtsh. u. Gynäk. **81**:382, 1919.
4. Holt, L. E., and Babbit, E. L.: J. A. M. A. **64**:287 (Jan. 23) 1915.

give the mortality figures of the first day, the first month and approximately for the first year. The early infant mortality of these children is absolutely accurate for very few have been lost sight of during the first month. From Table 2 it will be seen that the mortality rate for the first twenty-four hours lies between 9 and 13 per cent., or from 90 to 130 per 1,000 born; for the first week the rate lies between 14 and 20 per cent., or from 150 to 200 per 1,000 born.

TABLE 2.—MORTALITY DURING THE FIRST TWENTY-FOUR HOURS

Author	Cases	Deaths	Mortality, per Cent.
Ylppo	668	62	9.0
Schmitt	316	44	13.9
Schwarz and Kohn	272	29	10.5

TABLE 3.—MORTALITY DURING THE FIRST WEEK

Author	Cases	Deaths	Mortality, per Cent.
Ylppo	668	133	20
Schwarz and Kohn	272	39	14

The mortality figures for the first month are not so accurate. Tables 4 and 5 have been prepared from our own material and also from figures taken from the literature. For more accurate orientation we have grouped all the cases (Table 5) according to birth weight. Under 1,000 gm. the mortality rate is 940 per 1,000 born; from 1,000 to 1,500 gm. the mortality rate is 690 per 1,000 born; from 1,500 to 2,000 gm. it is 410 per 1,000 born, and from 2,000 to 2,500 gm. it is 110 per 1,000 born.

Summing up the mortality rate of the first month of life, it will be seen that 130 per 1,000 born, die during first day. From 150 to 200 die during the first week, and about 300 during the first month. Of 4,500 live born children from the same clinic [5] including those of normal and subnormal birth weight, there was a mortality rate of 10 per 1,000 for the first day, 15 per 1,000 for the first week and 26 per 1,000 for the first month. The rate is slightly better than the figures quoted from hospitals where undoubtedly more difficult cases are delivered and thus explain the slight increased rate; for instance, reports of Holt and Babbitt in New York and Kerness [6] in Munich, their mortality rate being 2.5 per cent. for the first week.

5. Schwarz, H.: Tr. Am. Soc. Prevention of Infant Mortality, 1914, p. 167.
6. Kerness, S.: Ztschr. f. Kinderheilk. Ref. **4**:19, 1913.

TABLE 4.—Mortality of the First Month in Relation to Birth Weight

Author	No. under 1,000 Gm.	Mortality, per Cent.	No. from 1,000 to 1,500 Gm.	Mortality, per Cent.	No. from 1,500 to 2,000 Gm.	Mortality, per Cent.	No. from 2,000 to 2,500 Gm.	Mortality, per Cent.	Total Number	Total Mortality, per Cent.
Crede[7]	...	..	24	83	15	36	54	11	93	31
Bakker[8]	9	100	75	88	138	34	502	10.5	724	16
Maygrier[9]	...	..	46	68	141	34	548	6	735	13
Schmitt[3]	15	100	48	80	113	41	83	11	273	13
Detre[10]	...	..	...	..	6	66.6	53	16	59	21
Ladd[11]	...	..	32	71.9	50	40	...	..	125	65
Budin, 1898-99 [12]	24	96	92	92	293	68.6	124	37	433	80
Ylppo[2]	37	83	183	48	240	23	208	14.9	668	30
Francois[13]	9	89	31	62	66	27	310	7	416	18.7
Schwarz	3	66	16	87.9	49	31	204	14	272	20

TABLE 5.—Mortality of First Month

Weight	Total Number Cases Selected from Literature	Total Number Deaths	Mortality, per Cent.	Mortality per 1,000 Pregnancies
Under 1,000 gm.	97	91	94	940
1,000 to 1,500 gm.	547	371	69	690
1,500 to 2,000 gm.	1,111	457	41	410
2,000 to 2,500 gm.	2,086	232	11	110
Total	3,841	1,151	30	300

TABLE 6.—Mortality for the First Year

Weight	Alive	Dead	Lost	Total Cases	Per Cent. Mortality of Known Cases
Under 1,000 gm.	1	2	0	3	66
1,000 to 1,500 gm.	3	10	3	16	77
1,500 to 2,000 gm.	11	22	16	49	50
2,000 to 2,400 gm.	84	47	73	204	36
Total	99	81	92	272	45

Table 6 shows the mortality for one year. Inasmuch as it was impossible to know the fate of all of our cases, we took the number known to be alive and those known to be dead and computed the mortality rate from these combined figures. Most likely, about the same percentage of mortality affected those lost to us. This table shows that 450 per 1,000 born, die before the end of the first year as compared with the general infant mortality rate of New York City of 90 per 1,000 born.

7. Crede, B.: Arch. f. Gynäk. **24**: 128, 1884.

8. Bakker, J.: Mitth. a. d. Hamburger Staats Krankenanstalt, 14 (Sept.) 1913.

9. Maygrier, C.: Obsteterique **12**: 290, 1902.

10. Detre, G. R.: L'avenir des prematures (etc.), Thésé de Paris, 1912.

11. Ladd, M.: Arch. Pediat. **27**: 416, 1910.

12. Budin, P.: Obstetrique **4**: 107, 1899.

13. Francois, M.: Caractére et elevage des prematures, Thésé de Paris, 1903.

MORTALITY IN RELATION TO PREMATURITY

From Table 7 it will be seen that prematurity is a most important factor in causing the high mortality in these cases. The premature cases have a mortality of 425 per 1,000 born as compared with 233 per 1,000 born in the full term cases. Single pregnancies premature, as compared with single pregnancies full term, show a mortality of 410 in the former to 157 in the latter, showing that prematurity is an important factor.

TABLE 7.—MORTALITY IN RELATION TO PREMATURITY

	Total Number Cases	Total Number Deaths	Mortality, per Cent.	Deaths per 1,000 Pregnancies
Single and Twin Pregnancies:				
Prematures........................	158	68	42.5	425
Full term.........................	114	27	23.3	233
Single Pregnancies:				
Premature........................	89	37	41.0	410
Full term.........................	69	11	15.7	157
Twin Pregnancies:				
Premature........................	69	31	44.3	443
Full term.........................	45	16	34.8	348
Premature Pregnancies:				
Single...........................	89	37	41.0	410
Twin.............................	69	31	44.3	443
Full Term Pregnancies:				
Single...........................	69	11	15.7	157
Twin.............................	45	16	34.8	348

Comparing premature twin pregnancies to full term twin pregnancies, there is a mortality of 443 per 1,000 and 348 per 1,000 in the latter. Here prematurity still shows its baneful effect, but not so markedly.

Discussing prematurity as to its effect on single pregnancies as compared with twin pregnancies, it will be seen that the mortality in the former (single) is 410 as compared with 443—not such a great difference—emphasizing that prematurity is more of a factor than twinning.

Finally, comparing full term pregnancies, that is single and twin, there is a mortality of 157 per 1,000 in the former and 348 per 1,000 in the latter (twin), showing that in these children twinning is not as deleterious as prematurity, yet gives only one-third the chance to life.

Of the many standards by which growth and development may be measured, gain in weight is probably the most reliable. Table 8 is the weight chart of eighteen cases with a birth weight under 2,000 gm., followed and weighed at different intervals during the entire first year. It is also interesting from the circumstance that some of the cases are from a social stratum in which all possible safeguards as to life and the best environment were obtained. The average birth weight of all the cases was 1,660 gm. The same children weighed 6,070 gm. at 6 months. This is a gain of 3,360 gm. for the first six months or a

gain of 764 gm. per month. This is a fair, or even a satisfactory gain for any infant at this period of life. At the end of the first year these children had an average weight of 6.690 gm., a gain of 1,920 gm. during the second six months of the first year, or 360 gm. per month, which is, perhaps, slightly below the normal monthly gain. Comparing the two social strata, it will be seen that those with the better niveau gained 1,440 gm. more during the first six months, and about 2,000 gm. more for the entire year. Yet neither one or the other made up for its deficiency at birth. The average gain for the last two months in utero, according to Friedenthal,[14] is something more than 1,920 gm., whereas these children gained 3,300 gm. or 3.25 kg., in the first six months of their extra-uterine life, and about 2,000 of these during the first two months. Thus the impulse seems to get weaker and weaker as these children get older, and it is a common experience that their weight chart becomes flatter after the first six months and, as we will show, still flatter from the twelfth and the eighteenth month. Most of these children were premature; thus the marked impulse to grow, characteristic of the last three months in utero, did not seem to persist.

WEIGHT

TABLE 8.—Weight Chart of Cases Under 2,000 Gm. Birth Weight

	Birth Weight, Gm.	Weight at 6 Mos., Gm.	Weight at 12 Mos., Gm.
Private material..........	1,440	6,480	8,940
	1,440	.....	6,100
	1,590	5,280	8,640
	1,680	5,340	7,680
	1,680	6,660	8,700
	1,860	5,520	8,240
	1,920	5,760	7,440
Clinic material............	990	4,260	6,090
	1,320	.....	5,280
	1,440	.....	5,340
	1,500	3,840	5,790
	1,680	6,510	7,770
	1,800	4,800	7,920
	1,830	3,480	3,930
	1,960	2,760	3,930
	1,920	4,200	5,820
	1,920	6,600	7,560
	1,920	.....	8,820
Average all cases..........	1,660	5,040	6,990
Average private cases.....	1,659	5,850	8,520
Average clinic cases........	1,661	4,410	6,540

We have observations on the weight of forty-nine cases with birth weight between 2,000 and 2,500 gm.; seventeen of these were of twin pregnancy and thirty-two of single pregnancy. The average weight

---

14. Friedenthal, H.: Ergeb. d. inn. med. u. Kinderheilk. **9**:505, 1912.

at six months was 5,800 gm. with a difference of only 180 gm. in favor of the twin pregnancy. At twelve months the average weight was about 8,000 gm. (16 pounds, 9 ounces), showing no difference whatever between the single and twin pregnancy. It would seem that the impulse to grow does not suffer because of twinning. These children gained about 3,500 gm. the first six months, which is about normal, and 2,200 gm. the second six months, which is within the normal. These children then, just as in the case of the still smaller ones, gain about what a child with a normal birth weight would, but do not exceed this and therefore do not catch up.

TABLE 9.—Weight Chart of Single Pregnancies with Birth Weight of from 2,000 to 2,400 Gm.

6 Months Gm.	1 Year Gm.	6 Months Gm.	1 Year Gm.	6 Months Gm.	1 Year Gm.
4,320	5,550	.....	7,740	.....	8,250
4,320	5,940	6,150	7,810	5,280	8,280
.....	6,240	.....	7,920	6,450	8,280
3,930	6,480	4,800	7,920	.....	8,880
4,980	6,540	5,160	8,070	7,200	8,940
5,490	6,810	.....	8,100	7,620	9,360
4,890	6,960	.....	8,160	.....	9,480
5,730	7,110	.....	8,160	6,480	9,540
5,910	7,200	6,480	8,220	7,170	9,540
.....	7,530	6,960	8,250	7,200	9,600
5,760	7,530				

Total number of cases, 32; average at 6 months, 5,760 gm.; average at 12 months, 8,010 gm.

TABLE 10.—Weight Chart of Twin Pregnancies with Birth Weight of from 2,000 to 2,400 Gm.

6 Months Gm.	1 Year Gm.	6 Months Gm.	1 Year Gm.	6 Months Gm.	1 Year Gm.
4,620	5,520	6,480	7,950	.....	8,460
5,160	6,960	.....	8,080	5,100	8,580
.....	6,600	6,060	8,220	6,630	8,760
.....	7,230	5,760	8,340	6,660	8,880
6,480	7,560	.....	8,370	.....	9,000
.....	7,700	6,120	8,430		

Total number of cases, 17; average at 6 months, 5,940 gm.; average at 12 months, 7,920 gm.

LENGTH

The growth in length is, perhaps, next in importance to the weight, yet hereditary factors probably play a greater rôle here. In the cases with a birth weight under 2,000 gm. (Table 11) none attained a height as great as the normal infant. The length at one year was never more than 64 cm., the average length of a five months infant. The weight at birth in the five cases observed seemed to have some relation to the length at one year, for the 990 gm. infant was the smallest in length. Although it was the smallest in length at the end of the year, it was as heavy as those with a length of 64 cm. The rate of growth during

the second six months in two cases was from 7 to 8 cm., equal to that of normal children.

TABLE 11.—Length Chart of Twin and Single Pregnancies with Birth Weight Below 2,000 Gm.

Birth Weight, Gm.	Length at 1 Month, Cm.	Length at 6 Months, Cm.	Length at 1 Year, Cm.	Weight at 1 Year, Gm.
990	34.4	53	60.9	6,150
1,440	..	..	64	5,340
1,800	..	..	64	5,340
1,920	49	55	63	6,810
1,920	..	..	64	.....

TABLE 12.—Length Chart of Single Pregnancies with Birth Weight Between 2,000 and 2,400 Gm.

Length at 6 Months, Cm.	Length at 1 Year, Cm.	Weight, Gm.	Length at 6 Months, Cm.	Length at 1 Year, Cm.	Weight, Gm.
..	60	5,550	..	69	9,390
..	63	.....	..	70	7,920
54	64	7,800	..	70	8,880
..	64	6,180	61	70	8,280
60	65	7,110	..	70	8,280
57	66	7,920	..	70	7,890
..	66	5,940	..	71	8,160
60.5	66.5	7,230	68	71.7	6,960
..	66.7	7,740	60	72	9,540
..	67	8,220	63	72	9,690
..	67	8,070	..	72	9,690
..	67	7,530	66.5	73	9,480
62	67.5	8,250	..	72	9,360
60	68.3	7.200			

Total number of cases, 28; average length at 6 months (11 cases), 61 cm.; average height at 12 months, 68 cm.

TABLE 13.—Length Chart of Twin Pregnancies with Birth Weight Between 2,000 and 2,400 Gm.

Length at 6 Months, Cm.	Length at 1 Year, Cm.	Weight, Gm.	Length at 6 Months, Cm.	Length at 1 Year, Cm.	Weight, Gm.
57	62	6,880	..	68	8,210
60	65	7,560	61	68.5	9,060
..	66	5,520	57	68.9	....
..	67	8,370	61	69	8,880
60	67	7,200	..	70	8,460
60	67.6	7,950			

Total number of cases, 11; average length at 6 months, 59.3 cm.; average length at 1 year, 67.3 cm.

In Tables 12 and 13 we have collected thirty-nine cases with a birth weight of between 2,000 and 2,400 gm., of which twenty-eight are from single pregnancies and eleven from twin pregnancies. At six months, seventeen of these thirty-nine cases have an average length of 60 cm.; about four are below the average of our general clinic material, and at one year showed an average length of 67.5 cm., as compared with an average of 73 cm. for the same type of child. It

appears that the growth in length lags about the same as the growth in weight during the entire first year. The growth in length of twins compared with those of single pregnancies shows the same phenomena as the weight figures, there being very little difference at any time. The impulse to grow in length for the first year is not strong enough to overcome the handicap at birth.

FURTHER DEVELOPMENT

The development of these children beyond the first year is naturally very interesting and important. Up to this period these cases do not make up what they had been deprived of at birth. Very few have

TABLE 14.—WEIGHT AND DEVELOPMENT OF CHILDREN WITH LOW BIRTH WEIGHT AFTER THE FIRST YEAR

Birth Weight	Age When Last Seen	Weight at One Year	Weight When Last Seen	Average Gain per Year after First Year	Length When Last Seen	Development and Remarks
2,200	15 mos.	.....	9,030	.....	...	General condition poor
2,200	15 mos.	.....	......	.....	...	Died of pneumonia
1,440	15 mos.	.....	......	.....	...	Died of pneumonia
1,680	17 mos.	8,700	10,680	3,900	...	Fair
1,860	17 mos.	8,220	9,660	2,800	...	Fair
1,680	18 mos.	7,680	9,420	3,480	...	Fair
1,830	18 mos.	3,960	7,770	7,660	...	Poor
2,300	2 yrs.	.....	11,580	.....	...	Good
1,440	2 yrs.	5,100	7,920	2,820	...	Poor
2,120	2 yrs.	9,120	11,640	2,520	...	Good
2,260	2 yrs.	.....	10,260	.....	...	Fair
2,400	2 yrs.	9,120	10,320	1,200	...	Fair
2,280	2 yrs.	.....	......	.....	...	Died of tuberculosis
1,920	2 yrs.	7,380	1,010	6,370	...	General condition fair
2,400	2 yrs.	.....	......	.....	...	General condition excellent
1,440	2 yrs.	8,940	10,740	1,800	81	General condition good
2,160	2 yrs.	.....	......	.....	...	General condition poor
2,160	2 yrs.	.....	......	.....	...	General condition excellent
2,160	2 yrs.	9,120	9,210	90	...	General condition fair
2,280	2 yrs.	.....	8,700	.....	70	General condition good
1,920	2 yrs.	8,820	8,580	"—"240	...	General condition poor
2,400	2 yrs.	.....	9,720	.....	73	General condition fair; 4 teeth
2,160	2 yrs.	.....	......	.....	...	General condition good
2,160	2½ yrs.	.....	13,200	.....	86	General condition excellent
1,500	2½ yrs.	5,760	9,360	400	76	General condition fair
1,800	3 yrs.	9,600	14,400	2,400	...	General condition fair
2,400	3 yrs.	.....	......	.....	...	Does not talk, walked at 2 yr.
1,320	3½ yrs.	7,380	10,140	740	83	General condition poor; Hb. 28 per cent.
2,400	3½ yrs.	.....	......	.....	...	Stupid; does not walk
2,400	4 yrs.	7,740	13,080	1,780	89	Excellent
2,040	4 yrs.	6,360	10,560	1,400	91	Fair
1,680	4 yrs.	.....	......	.....	...	General condition good
1,920	5 yrs.	9,240	27,480	4,560	...	General condition good
2,400	5 yrs.	.....	......	.....	...	General condition good
2,400	6 yrs.	.....	19,680	.....	...	Excellent
2,160	6 yrs.	.....	......	.....	...	Excellent
2,400	6 yrs.	.....	......	.....	....	Excellent
990	6 yrs.	5,880	21,600	3,144	117	Good
2,160	10 yrs.	6,900	19,140	1,360	114	Good

attained an approximately normal weight or length. Table 14 shows the follow-up of thirty-nine cases. Seven cases were followed for from fifteen to eighteen months; eighteen, from two to three years; seven, from three to four years; six, from five to six years, and one was followed for ten years.

Of the seven cases followed from fifteen to eighteen months, two had died of pneumonia; only one infant had reached an approximately normal weight (10.68 kg.); two were in very poor general condition, and three were rated as fair. The weights of these ranged from 7 to 9 kg. (15 to 19 pounds). Of the eighteen cases followed from two to three years, one died of tuberculosis; three were in poor condition; six were rated fair, and eight, about 50 per cent., were in good physical condition. We have been able to secure the weights of thirteen of these cases. Only three of them can be called normal (11.6, 11.6 and 13.0); five weighed from 7 to 9 kg. and from 9.6 to 10.5 kg., all decidedly under weight. Thus of the preceding twenty-five cases only four had reached their normal weight in or before the fourth year. We have the growth in length in five cases, two measuring 81 and 86 cm., well within the average for this age; the remaining three were between 70 and 76 cm., distinctly below the normal of a 2 to 3 year old child.

We have followed nine cases from four up to six years. Two of these are mentally subnormal; one is in very poor physical condition; two are rated fair, and four are in good physical condition.

The weight in five of these cases was obtainable and found to be normal in only one case (27.5 kg.); the others weighed 14.4, 10.1, 13.4 and 10.5 kg., respectively. We have the lengths of three of these children. They ranged from 83 to 91 cm. for $3\frac{1}{2}$ and 4 year old children, which is, perhaps, not quite up to normal, but nearly so. We have records of five cases above 6 years, all in good condition. The weights are normal, except in the 10 year old child, whose stature is very small (114 cm.), but whose general condition is good.

The column in Table 14 showing average gain per year is extremely interesting, for it will be seen that in most cases the average gain is above the normal. As shown before, this is not true of the first twelve months where the gain is either about the average, normal or less. It would seem, therefore, that these children gain slightly above normal the first six months. After the first year these children gradually make up the deficiency in weight, but rarely do they attain the normal weight before the end of the fourth year (5 in 25). This is in accord with the finding of Ylppo.[2] The gain in weight does not keep pace with the gain in length however, for although we have not enough data for a positive statement, this deficiency in length is made up before that of the weight.

SUMMARY

From 2 to 5 per cent. of all viable births result in children of low birth weight.

The mortality rate during the first month in this type of case is ten times that of the normal.

The lower the birth weight, the greater the mortality.

The mortality rate for the year in this type of case is four and one-half times the normal.

In these children of low birth weight the mortality is twice as great in the premature as in the full term.

Twinning in the premature does not markedly affect the mortality rate.

In the full term, the single pregnancy has twice the chance for life as compared with the twin pregnancies.

The gain in weight during the first twelve months is at the same rate as that of the normal child, so that the deficiency is not made up at the end of the first year. Twins do not act differently than those from single pregnancies.

The growth in length is not made up during the first twelve months.

These children seem to attain the normal in length sooner than the normal in weight. It is only before the end of the fourth year that they compare with children of normal birth weight.

The general condition and mentality seem to be that of normal children through infancy and early childhood, although they have a greater tendency to anemia and rickets.

EFFECT OF A RATION LOW IN FAT SOLUBLE "A" ON THE TISSUES OF RATS[*]

MARGUERITE DAVIS AND JULIA OUTHOUSE

MADISON, WIS.

It is an established fact that the fat soluble vitamin is necessary in the ration. Drummond[1] reported a lowered resistance to infection in rats deprived of this vitamin. He found, however, no specific pathologic change on gross examination of grown or half grown rats. Emmett[2] states also that in a histologic examination of rats fed a ration deficient in the fat soluble vitamin he found the tissues normal. He does not give the age of the animals.

On the other hand, Tozer[3] found that young guinea-pigs on a ration deficient in the fat soluble vitamin, even with an excess of the antiscorbutic vitamin, develop enlargements of the costochondral junctions very similar to the beadings of scurvy.

M. Mellanby,[4] who worked with puppies, found that the fat soluble vitamin controlled the calcification of the teeth. With a ration of white bread and 200 c.c. skimmed milk daily, the shedding of the deciduous teeth was retarded, the development of the permanent dentition was delayed, the arrangement of the teeth in the jaws was poor, and the calcium content of the teeth was subnormal. The teeth of the more rapidly growing puppies were worse. If the puppy was over 3 months old when put on the ration, the teeth were not affected to any degree.

E. Mellanby[5] has shown that the fat soluble vitamin is largely responsible for the calcification of bone. With the bread and skimmed milk ration, puppies developed a beading of the ribs. This is more marked in puppies one month old than in those 6 weeks old. After eight weeks they failed to develop the beaded rib. This lesion appears to be outgrown in time, and resembles the condition of rickets in children.

The two lines of investigation which we have followed are: (1) a long time experiment with a ration low in the fat soluble vitamin but satisfactory in other respects; (2) an experiment with young animals on a ration low in the fat soluble vitamin. We are not as yet ready to report the results of the second experiment.

1. Drummond: Biochem. J. **13**:95, 1919.
2. Emmett: J. Biol. Chem. (Proceedings) **41**: liii, 1920.
3. Tozer: Quoted by Delf, Biochem. J. **14**:212, 1920.
4. Mellanby, M.: Lancet **2**:767, 1918.
5. Mellanby, E.: Lancet **1**:407, 1918.

It was necessary to choose a ration which was eaten readily, for there are marked pathologic changes in inanition. Jackson[6] found that a limited amount of whole wheat bread and whole milk produced definite changes in the suprarenal of rats. McCarrison[7] reports a profound effect of inanition on the gastro-intestinal tract of monkeys which had refused to eat a diet of autoclaved rice. In fowls he found hypertrophy of the suprarenal with an increased amount of epinephrin. Other organs were greatly atrophied.

TABLE 1.—COMPARISON OF WEIGHTS OF ORGANS OF DONALDSON'S AND AUTHORS' EXPERIMENT ANIMALS

	Age	Body Weight, Gm.	Two Kidneys, Gm.	Spleen, Gm.	Testes, Gm.
Donaldson............................	...	204.3	1.74	0.545	2.203
No. 15..............................	114	203.0	2.0*	1.0*	2.8
Donaldson............................	...	178.1	1.544	0.479	2.030
No. 15..............................	114	178.0	1.3	0.65	2.5
Donaldson............................	...	175.0	1.521	0.471	2.007
No. 15..............................	114	174.0	1.6	0.9	1.0†

* Enlarged spleens are common in stock rats.
† Only one testes found.

TABLE 2.—GROWTH OF SECOND GENERATION BORN ON THE RATION

Serial No. of Litter	Age at Death, Days	Maximum Weight, Gm.	Normal Weight, for Age, Gm.
26	101	89	165
	60	26	77
	50	32	59
	100	98	165
	70	51	104
	60	40	80
	40	20	43
	75	64	118
	70	42	98
	90	71	150
	50	22	59
27	Discontinued at 25 days	32	25
	Discontinued at 25 days	35	25

Rats were employed because the span of life is shorter and we desired to continue the ration through as many generations as possible. The ration consisted of crushed oats, polished rice and skimmed milk ad libitum, and a limited amount of cooked potato and egg white. On this ration, the half grown males grew at from 80 to 90 per cent. of the normal rate for three months. After a period of maintenance, they became emaciated and died. None lived longer than eight months.

Most of the females reared one litter and a few reared two litters on the ration. All but three of the litters were born in the first two

---

6. Jackson: Am. J. Anat. **21**:321, 1917.
7. McCarrison: Indian J. M. Res. **7**:269, 1919.

months. A second litter of four young was born when the mother had been 148 days on the ration.

One of the four was a female. She reared a litter of two young. She was 135 days old at parturition, which made 283 days since the beginning of the experiment. When the young were twenty-five days old, they were discontinued. This made 308 consecutive days for the three generations.

Of the twenty-three females born and continued on the ration, seven produced litters. Only two of these litters were reared. There were eleven young in one litter. They were born when the mother was 131 days old and 144 days after the original rats were put on the ration. Two of the eleven lived 101 days, which made a total of 285 days of the experiment.

Distended abdomens were conspicuous in all of the young born on the ration. In some cases this disappeared after four or five months. Xerophthalmia, which Osborne and Mendel[8] and McCollum and Simmonds[9] reported in the absence of the fat soluble vitamin, appeared at from four to five months in the rats born on the ration. In less than 200 days, all of the animals had either died or were chloroformed in an emaciated condition. Three rats born on the ration were killed when they were still growing and in good condition. The testes, kidneys and spleen were weighed, and the weights were compared with those given by Donaldson[10] for rats of the same weight. Table 1 shows that these organs are of about normal weight.

In the litter of eleven young of the second generation born on the ration, in addition to the distended abdomen and xerophthalmia, small hemorrhagic spots appeared on the tails, and when the rats were about 30 days old the ends of the tails dropped off. The eyes were pale and a blood count showed from 4,000,000 to 5,000,000 red blood cells in contrast to a normal count of 8,000,000. Table 2 gives the growth in this generation.

A postmortem examination of the rats put on the ration, as well as of those born on the ration, showed the stomach and intestines filled with gas, the intestines dull and brown, and no intraperitoneal fat visible.

Necropsy of the second generation born on the ration revealed very marked anemia. The lungs were white and the liver and kidneys were sand color. The bones were very fragile. There was no apparent beading of the ribs.

A histologic examination was made on rats from most of the litters. The organs examined were: heart, spleen, liver, lung, pancreas, kidney

8. Osborn and Mendel: J. Biol. Chem. **16**:431, 1913.

9. McCollum and Simonds: J. Biol. Chem. **32**:347, 1917.

10. Donaldson: Memoirs of Wistar Institute of Anat. and Biol., No. 6, 1915.

and testes. The tissues were removed immediately at necropsy and fixed in Zenker's fluid, embedded in paraffin, cleared in xylol, and stained with hematoxylin and eosin. This stain gives only the marked differences. Differential stains were not used.

TABLE 3.—RESULTS OF HISTOLOGIC EXAMINATION OF ORGANS

Lot No.	Animal No.	Days on Ration	Kidney	Spleen	Lung	Heart	Pancreas	Liver
7	3	227	Cloudy swelling	Dilated venous sinuses	*	*	Normal	Normal
8	4	227	Cloudy swelling	Dilated venous sinuses	..	*	Normal	Normal
5	6	217	Slight congestion	Congestion	Congestion	Normal	Normal	Normal
7	6	217	Albuminous precipitation in tubules, slight congestion	*	*		Normal	Normal	Normal
9	9†	93	Slight congestion, albuminous precipitation in tubules	Congestion	Normal	Normal	*	*
15	10†	115	Cloudy swelling	....	Normal	Slight atrophy of parenchyma	Normal	Normal
	12	115	Cloudy swelling, albumin in tubules	Congestion, dilated venous sinuses	*	*	Normal	..
	14	181	Cloudy swelling, albumin in tubules	Congestion, dilated venous sinuses	*	*	Normal	Normal
18	25†	178	Cloudy swelling, congestion	Extreme congestion	Normal	Normal	Normal	Normal
	26†	178	Cloudy swelling, albumin in tubules	*	*	Normal	Normal	*
	27	178	Cloudy swelling, albumin in tubules	Dilated venous sinuses, slight destruction of tissue	*	Normal	*	*
26	30†	70	Extreme cloudy swelling, cells of tubules skeletonized	Congestion	Bronchopneumonia	Normal	Nuclei indistinct	Absence of red blood cells
	31†	70	Extreme cloudy swelling, cells of tubules skeletonized, glomeruli shrunken	Congestion	Bronchopneumonia	Normal	Normal	Absence of red blood cells

* Not eexamined.
† Testes in Animals No. 9, 10, 25, 26, 30 and 31 were normal; testes of other animals not examined.

The examination showed that there were very few changes in the tissues on this ration. The heart, pancreas, liver and testes remained normal in most cases. Slight changes were found in the kidney and spleen. Congestion and chronic inflammation was frequently found,

indicating, in all probability, a secondary infection, although an effort was made to discard without microscopic examination all those which gave evidence of infections of the respiratory tract.

Liver: The liver appeared to be normal in all cases. Necrotic and degenerative changes were absent. In Lot 26 there was a total absence of red blood cells. Otherwise the structure was normal.

Spleen: The spleen showed very slight changes. There was congestion with frequent dilation of venous sinuses. In some the congestion was so marked as to mask the structure. Necrosis or degeneration of splenic reticulum was not observed. There seemed to be no relationship between the degree of congestion and the duration of the experiment.

Kidney: The main finding in the kidney was cloudy swelling of the parenchyma of the collecting tubules. This was more marked in the tissues of the second generation born on the ration. An albuminous precipitate was present in the tubules of some. Congestion also was found. The kidneys of Lot 26 were most affected. In places the cells of the tubules appeared skeletonized, and the glomerular tufts were slightly shrunken.

The results of the histologic examination are shown in Table 3. Lots 5, 6, 7, 8 and 9 were fed on the ration when half grown. Lots 15, 16, 17, 18 and 19 were born on the ration. Lot 26 was born from Lot 15.

GANGRENE OF TOES IN AN INFANT, DUE TO SCALD *

GEORGE DAVID CUTLER, M.D.

BOSTON

The case reported herewith is of interest first, because of the etiology, and, secondly, because of the satisfactory end result of conservative treatment.

REPORT OF CASE

History.—An infant, 5 days old, was seen in consultation for gangrene of the toes of the left foot which had resulted from a scald during delivery. The mother had been advised to sit over a pan of hot water to hasten parturition. While doing so a foot presented and was scalded.
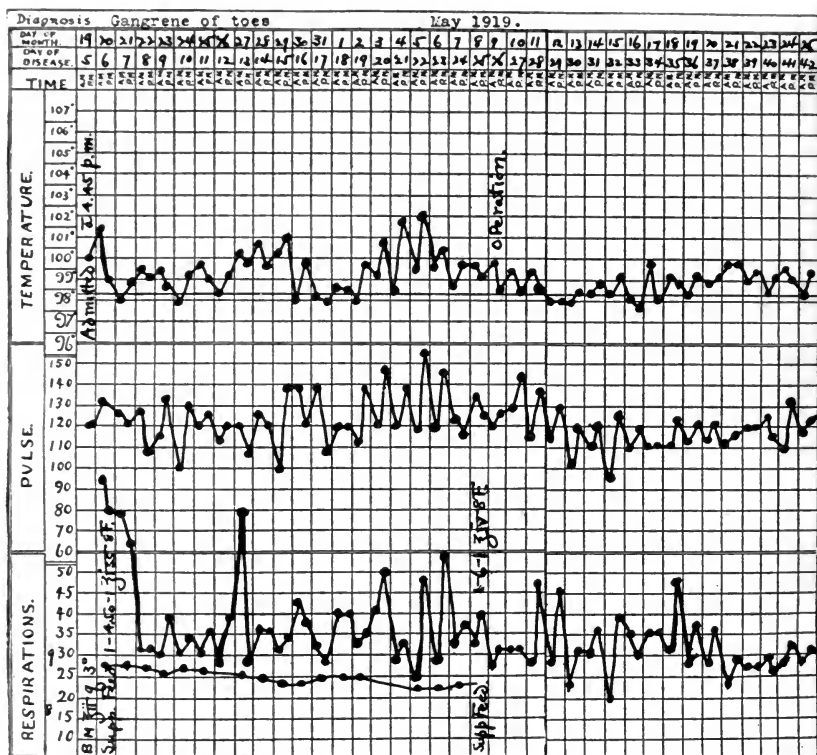
Fig. 1.—Clinical record.

Examination.—The left foot showed a scald of the second and third degree extending up above the ankle on the anterior surface. Gangrene extended to Chopart's line. The infant appeared otherwise normal and was not prostrated.

Fig. 2.—Appearance of the foot at entrance to hospital five days after scald.
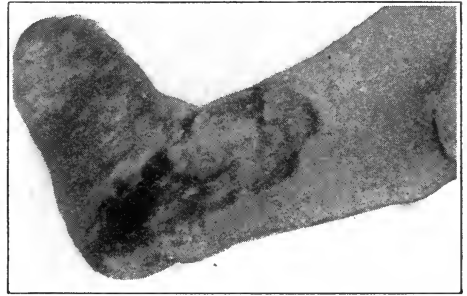
Fig 3.—Cast of toes sloughed twelve days after scald.

Fig. 4.—Dorsal view of slough.
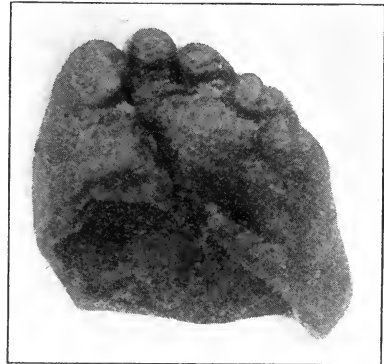
Fig. 5.—Plantar view of slough.

Fig. 6.—Proximal end view of slough showing ends of phalanges.

Fig. 7.—Print from a roentgenogram to show separation of phalanges from foot.

Treatment.—It was considered advisable to send the baby to the Children's Hospital for treatment. After consultation with other members of the staff it was decided to proceed conservatively, avoiding amputation if possible. The foot was placed on sterile towels for open air treatment, and attention was directed to the patient's general condition.

The baby entered the ward May 19, 1918, and its condition was satisfactory after the second hospital day. One week later, the five toes came off as a cast, leaving a healthy granulating surface. Feedings were well taken and normal weight was maintained. The first week in June, a swelling was noticed above the right knee, which increased in size fairly rapidly and became fluctuant. It was assumed to be a metastatic abscess. The roentgen-ray examination of the knee and thigh showed no bone involvement. The abscess was incised and drained under ether anesthesia June 9. A large amount of pus was evacuated. By June 16 there was no more drainage. June 25 the patient was discharged with the incision in the thigh healed and the granulating surface on the left foot was healing well under boric acid ointment dressings.

Result.—A note from the mother, dated August 6, states that the foot is entirely healed. The baby weighs 11 pounds and is well and happy.

COMMENT

Infectious and noninfectious gangrene may occur in infants and children. It may be caused by (1) traumatism of various kinds, including the accidental strangulation of parts; (2) local action of chemicals; (3) disorder of the nervous system, as in Raynaud's disease; (4) constitutional diseases, i. e., hemophilia, purpura and diabetes; (5) thrombosis and embolism; (6) infection by bacillus of malignant edema or other organisms; (7) a combination of morbid influences, often a mixed infection, complicating or following such diseases as scarlet fever, measles, diphtheria, varicella, erysipelas, typhoid, and other fevers; (8) ecthyma gangrenosa. In short, as Kelley states,[1] the possible causes in children include all those which produce the disease in adults, except senile changes.

The interesting point in the case reported is the conservation of a useful foot by allowing the gangrenous tissues to slough rather than removing them by amputation. The abscess of the right thigh was presumably metastatic from the slightly infected granulations of the stump, as the umbilicus was clean and no other focus of infection was present.[2]

1. Kelley, S.: Surgical Diseases of Children, 1914, p. 148.

2. The following references may also be consulted:

Michael, M.: Am. J. Dis. Child. **20**:124 (Aug.) 1920.

Graham: Diseases of Children, Philadelphia, Lea & Febiger, 1916, pp. 601, 580, 125, 649.

Kerley: Practice of Pediatrics, Philadelphia, W. B. Saunders Co., 1914, pp. 356, 496.

Holt: Diseases of Infancy and Childhood, New York, D. Appleton & Co., 1916, pp. 286, 258, 413, 505, 552, 969, 985.

Stelwagon: Diseases of the Skin, Philadelphia, W. B. Saunders Co., 1915, p. 427.

MALT SOUP EXTRACT AS AN ANTISCORBUTIC *

H. J. GERSTENBERGER, M.D.

CLEVELAND

During 1918, while studying the respiratory quotient of scorbutic infants, we decided for definite reasons to feed these infants with Keller's malt soup, a mixture containing 100 gm. of the so-called malt soup extract, which has made for itself a record of producing and never of curing scurvy. Hess,[1] for instance, reports that in his experience the malt soup preparation is the diet which has been associated with scurvy most frequently. September 6, 1918, a patient who had developed a scurvy in another institution on Keller's malt soup was given the same kind of a mixture in pursuance of the above stated aim, but on the fourth day orange juice was added to the diet, and so the surprise which we were to have later in the case of another patient was inadvertently postponed. September 26, 1918, another scorbutic patient, 11 months of age, was brought to the hospital with a history of poor development and bad stools (Table 1). He was bottle-fed since birth. From the age of 1 month on until he was 10 months old he was fed a mixture of one-half milk and one-half oatmeal water with cane sugar. Then he received for another month two-thirds milk and one-third oatmeal water. During this month he suffered from diarrhea, and as a result, the stepmother, who took charge of him at this time, frequently gave him castor oil, but without beneficial effect on the painful lower extremity. The physical examination showed a decided case of scurvy, the patient having swollen and bleeding gums about the upper and lower incisors, enlarged epiphyses, a rosary, an enlarged spleen, and increased permeability of capillaries, a swollen right knee and a very sensitive left knee. For our purposes of respiratory quotient study he was also put on Keller's soup. On the day of his admission to the hospital he received a mixture of one-half skimmed milk and one-half oatmeal, and on the following day he was offered Keller's soup, but refused most of it, taking only a total of 250 c.c. On the next day, however, he took 820 c.c. and then the full 1,000 c.c. offered him. We expected no improvement, and as we wished to see the effect of the

1. Hess, Alfred F.: Infantile Scurvy. V. A Study of Its Pathogenesis. Am. J. Dis. Child. **14**:347 (Nov.) 1917.

orange juice on the respiratory quotient and as we also wished to have the same carbohydrate intake in the preliminary period as would occur in the regular period, we gave him, besides 1,000 c.c. of Keller's soup, 60 c.c. of a 10 per cent. solution of sugar, composed of 6.5 per cent. of glucose and 3.5 per cent. of sucrose. The higher percentage of glucose was used because levulose was not available.

TABLE 1.—ANALYSIS OF CLINICAL HISTORY OF SECOND SCURVY PATIENT

Date, 1918	Food		Weight, Gm.	Temperature			Stools	Clinical Condition and Symptoms
	Kind	Amt., C.c.						
Sept. 26	Skimmed milk ½, OMW ½	600	.....	38.1	37.6	27.6	E	Pallor; restless; bleeding and swollen gums about incisors; right knee swollen and very sensitive, left also sensitive. Child also showed a marked rosary, enlarged spleen and epiphysis on admission; had diarrhea for a long time before admission
Sept. 27	Skimmed milk ½, OMW ½	100	5,610	38.2	37.8	37.9	1 T	Same
	Keller's soup	250						
Sept. 28	Keller's soup	820	5,480	37.0	37.3	38.0	3 T	No change noticed
Sept. 29	Keller's soup	1,000	5,550	37.9	37.6		3 T	No special observation made
Sept. 30*	Keller's soup	1,000	5,725	36.6			2 N	
Oct. 1	Keller's soup	1,000	5,855	36.8			1 T	Child's improved disposition noted
Oct. 2	Keller's soup	1,000	5,845	37.0	37.4		2 N	Gums normal; joint sensitive and swelling gone
Oct. 3	Keller's soup	1,000	5,800	37.0	37.6		5 N	Same; very happy; looks much better
Oct. 4	Keller's soup	1,000	5,790	37.2	37.6		4 N	Same; joints negative to pressure
Oct. 5	Keller's soup	1,000	5,800	37.4	37.6		3 N	Continued general improvement
Oct. 6	Keller's soup	1,000	5,800	37.9	37.9		2 N	
Oct. 7	Keller's soup	825	5,790	37.0	37.2		1 SN	
Oct. 8	Keller's soup	100	5,900	37.2	37.2		2 T	
Oct. 9	Keller's soup	100	5,970	37.0	37.0		1 SN	
Oct. 10	Keller's soup	100	5,945	36.8	37.8		2 N	
Oct. 11	Keller's soup	100	5,900	37.2	36.2		1 SN	
Oct. 12	Keller's soup	100	5,950	37.4	37.4		2 SN	Color better

* September 30, the patient received 60 c.c. of a 10 per cent. sucrose solution; October 1 to 7, inclusive, 90 c.c. of a solution containing 3.5 per cent sucrose and 6.5 per cent. glucose daily; October 8 and 9, 660 c.c. and October 10, 11 and 12, 90 c.c. of the same solution daily.

October 1, it was noticed that the child seemed different, but no particular attention was paid to the scorbutic symptoms, simply because we did not expect any special change. October 2, however, the child seemed so normal that an accurate inspection of the gums was made, and to our great surprise these were found to be absolutely normal. The swelling of the right knee joint had lessened, and the sensitiveness of both the left and the right knee had practically gone. With each succeeding day the child improved in general appearance and disposition, so that we could say definitely that the child had been cured of scurvy, at least of the severe, active stage of scurvy. This experience was so remarkable that nothing was said about it and observations were made to determine whether through some error the child had not

received an antiscorbutic. No evidence in this connection was discovered, however, and so it was decided to say nothing and wait for the next opportunity, which came Dec. 13, 1918.

This third patient had an enormous hematoma of the right femur, and after three days of half milk, half oatmeal water, and $2\frac{1}{2}$ per cent. of cane sugar, the child was given Keller's soup, prepared with the same malt extract that had been used in the previous cases. The gums of this child were perfectly normal, and we had to depend entirely on the sensitiveness and the size of the large swelling to decide whether we had much improvement or not. After three days' observation there was no definite and positive improvement, and as the child was quite ill and had a temperature of 38.5 C., and as the respiratory quotient curves showed certain interesting features, we decided to give orange juice at this time, with the result that within a few days the child showed a distinct improvement. But the improvement was gradual, even with 90 c.c. of orange juice in twenty-four hours, so that, after all, we did not know from his experience whether or not the Keller's soup or the malt extract in the Keller's soup had also exerted any antiscorbutic influence in this child. So again we decided to wait for another opportunity, which came Dec. 30, 1918.

This fourth patient, a colored infant, 10 months of age, was brought to the hospital with a history of stomach trouble and swollen feet (Table 2). She had been artificially fed since the third week, at first for six weeks with a milk dilution, then for six months with bread and tea, and finally during the last three months with a cane sugar one-half milk and one-half water mixture. On physical examination the child showed a very marked rosary and a decided swelling of the lower extremities—especially below the knees. All the tissues about and especially above the right ankle were very much indurated, and all of these swollen areas were extremely sensitive to the slightest pressure. The child objected to moving its legs and was very unhappy and irritable. The gums showed no lesions, even though too small lower incisors had just erupted. This finding is not so very uncommon in cases of scurvy, especially as regards the lower incisors, and in no manner speaks against the correctness of the diagnosis of this case. We have had occasion to see undoubted symptoms of scurvy develop, when the gums of both the lower as well as of the upper incisors were normal. It is unquestionably true, however, that swollen, bleeding, bluish-red gums are the most dependable and characteristic sign of infantile scurvy. The epiphyses at the wrists were only slightly enlarged. After three days feeding with two-thirds milk and one-third oatmeal water, with 3 per cent. cane sugar, during which time no improvement was noticed, she was given Keller's soup made up with the same malt soup extract that had been employed for the last two cases. Ninety c.c. of artificial

orange juice were also given. The next day, January 3, the infant seemed to be passing more urine, and especially was this difference noted the following day. No attempt, however, was made to get an accurate record of the amount of urine excreted, as the patient was a little girl. After twenty-four hours of Keller's soup the child's disposition seemed to be changed for the better, and January 5 there was a marked reduction in the sensitiveness to pressure on the knees, the

TABLE 2.—ANALYSIS OF CLINICAL HISTORY OF FOURTH SCURVY PATIENT

Date, 1918	Food		Weight, Gm.	Temperature			Stools	Clinical Condition and Symptoms
	Kind	Amt., C.c.						
Dec. 30	OMW ⅓, milk ⅔, cane sugar 3%	700	.....	37.3	37.5	37.1	...	Marked fretfulness and restlessness; pain on the slightest movement of lower extremities; decided swelling and induration of tissue above knee and especially below; marked sensitiveness to slightest touch; gums normal. Child shows a very marked rosary
Dec. 31	OMW ⅓, milk ⅔, cane sugar 3%	900	5,370	37.6	37.2	37.6	1 N	Same
Jan. 1	OMW ⅓, milk ⅔, cane sugar 3%	700	5,370	38.0	37.1	37.6	1 N	Same
Jan. 2*	Keller's soup	900	5,175	36.4	36.6		3 N	Same
Jan. 3	Keller's soup	900	5,145	36.6	37.2	36.6	6 SN	Disposition seems better; urinates more
Jan. 4	Keller's soup	900	5,130	36.2	36.5		3 SN	Seems more comfortable; urination much incr.
Jan. 5	Keller's soup	900	5,100	36.6	37.5		3 SN	Less sensitive; wet all the time
Jan. 6	Keller's soup	900	5,130	37.0	37.2		3 SN	Swelling practically gone; sensitive only to deep pressure; happy
Jan. 7	Keller's soup	900	4,925	36.6	37.4		2 N	Laughs and is contented; still very wet
Jan. 8	Keller's soup	900	4,905	36.5	36.6		2 N	Legs show no swelling whatever; no pain even on deep pressure; seems entirely well
Jan. 9	Keller's soup	900	4,870	36.5	37.2		4 N	
Jan. 10	Keller's soup	900	4,840	36.1	37.2		2 N	
Jan. 11	Keller's soup	900	4,900	36.1	37.1		2 N	
Jan. 12	Keller's soup	900	4,850	36.0	36.5		2 N	
Jan. 13	Keller's soup	900	4,910	36.6	37.6		2 N	
Jan. 14	Keller's soup	900	4,850	36.1	37.0		3 T	
Jan. 15	Keller's soup	900	4,910	36.6	37.3		1 N	
Jan. 16	Keller's soup	900	4,800	36.5	37.3		1 N	
Jan. 17	Keller's soup	900	4,990	36.8	38.0	36.0	2 N	
Jan. 18	Keller's soup	900	4,990	36.5	37.5		1 N	Pertussis vaccine; left knee and right ankle sensitive to pressure; is fretful. Due to effects of vaccine injection

* From January 2 to 8, inclusive, the patient received 90 c.c. of artificial orange juice daily and from January 9 to 18, 90 c.c. of orange juice daily.

tibiae and the ankles. January 6 there was an enormous improvement, the legs being sensitive only to every deep pressure, the swelling and induration having practically disappeared. The baby moved its legs about and appeared to be all right. January 8 no swelling whatsoever could be found, and even severe pressure brought no response; the baby laughed and was very happy and contented. So that in this case we

can maintain that the child was definitely cured without receiving orange juice or any other hitherto known antiscorbutic. January 9 orange juice was given for respiratory quotient study, but no further change in the condition of the child was noticed, except on the eighteenth, when the child received an injection of pertussis vaccine and as a result developed fever and, what is interesting, a sensitiveness of the left knee and of the right ankle. This renewed sensitiveness, however, disappeared within a few days, and evidently had some direct connection with the injection of the pertussis vaccine.

TABLE 3.—ANALYSIS OF CLINICAL HISTORY OF FIFTH SCURVY PATIENT

Date, 1919	Food		Weight, Gm.	Temperature			Stools	Clinical Condition and Symptoms
	Kind	Amt., C.c.						
May 10*	S. M. A.	250	.....	....			1 SN	Pallor, fretfulness, marked swelling of right ankle and thigh; knees and ankles sensitive to slightest touch; suppurating hematoma in right buttock. Râles at both bases
May 11	S. M. A.	490	7,170	39.7	38.8	39.6	2 SN	Same
May 12	S. M. A.	390	7,340	40.2	38.0	39.0	3 SN	General condition decidedly better; no local change
May 13	S. M. A.	690	7,260	37.7	39.4	38.4	2 SN	Much improved generally; looks about
May 14	S. M. A.	790	7,220	39.0	38.5	37.5	3 SN	Marked increase in urination; even more comfortable. Still breaths rapidly, looks "pneumonic"
May 15	S. M. A.	970	7,430	39.4	38.8	39.2	3 SN	Marked increase in urination; swelling of right ankle gone entirely; legs can be moved with little discomfort; tries to smile. Pseudolabor pneumonia at left base
May 16	S. M. A.	960	7,210	38.3	39.4	37.7	5 T	Right ankle also much reduced; sensitiveness of joints practically gone; smiles. While scorbutic symptoms have markedly improved, pneumonic picture remains unchanged
May 17	S. M. A.	970	7,290	39.5	38.4	38.6	5 T	Child moves legs about of own accord without pain; no tenderness except in right hematoma area
May 18	S. M. A.	900	7,330	38.4	39.5	38.0	3 T	Is interested and can smile
May 19	S. M. A.	905	7,620	39.5	39.5	38.0	3 T	
May 20	S. M. A.	960	7,550	37.0	37.6	38.2	3 T	Pneumonia picture changed
May 21	S. M. A.	950	7,340	37.4	37.4	36.8	5 SN	Pneumonia picture gone
May 22	S. M. A.	1,000	7,320	36.9	37.0	37.1	1 N	
May 23	S. M. A.	990	7,330	37.0	36.8	36.4	4 SN	Right thigh still slightly tender; healing of suppurative hematoma. Looks fine; seems very well; few râles still present at left base
May 24	S. M. A.	985	7,340	36.6	37.2	37.5	6 SN	
May 25	S. M. A.	985	7,295	36.8	36.9	37.5	5 SN	
May 26	S. M. A.	885	7,295	36.8	37.4	37.7	8 SN	

* May 10, the patient received 60 gm. of malt soup extract, and from that day on, 100 gm. daily.

May 10, 1919, a fifth baby, 8 months old, was brought to Lakeside Hospital with a diagnosis of osteomyelitis (Table 3). The mother stated that the child had been coughing for two weeks, and had also developed at about that time a large swelling on the right buttock, which was opened by a physician. While this wound had drained quite

well, the tumor below the abscess seemed to get larger and more tender. The patient was admitted on the surgical service and then taken over to the pediatric service with a diagnosis of scurvy. The right thigh between the knee and hip was markedly swollen and the old incision was still oozing slightly. Both knees and the right ankle were especially sensitive, also the left ankle, but not as much as the other three joints. Around and especially above the right ankle there was marked and hard induration, and through the skin bluish areas could be seen. The child was pale, had a marked rosary of the "necropsy chest" type, enlarged epiphyses at the wrists, was very fretful, laid in a frog fashion, and would cry severely as soon as its lower extremities were moved.

Instead of giving this child Keller's soup we gave it S. M. A. (synthetic milk adapted) in order to exclude the possible therapeutic effect of the one-third certified milk that had been used in the Keller's soup for the other children recorded above. A large batch of 20 quarts of S. M. A. was made at one time and prepared over the regular route of pasteurization. We offered the child 1,000 c.c. of S. M. A., but inasmuch as its appetite was very poor we had to resort to gavage after a few days. The antiscorbutic value of S. M. A. is small, and not adequate to prevent a normal child that is getting nothing but S. M. A. from developng scurvy, so that any therapeutic effect obtained by the giving of S. M. A. could not be explained by its administration. Therefore, in this case we gave the malt soup extract, a part of the same lot that had been used for the preparation of the other Keller's soup mixture used in the previously described cases, in the same amount in which it had been administered in the form of Keller's soup, namely, 100 gm. for each twenty-four hours. May 11, the child received 60 gm.; May 12, 100 gm., and after that 100 gm. daily were given of the malt soup extract in addition to the 1,000 c.c. of S. M. A. At first the malt soup extract was given separately, later on it was mixed with the S. M. A., just before it was offered to the child, and so it was not exposed to a temperature above 37 C. The subjection of this malt soup extract to a higher temperature would have made no difference, however, because it was exposed to boiling temperature in all of the previous cases, and in all but the last to an additional temperature above 100 C., but it still retained sufficient antiscorbutic value to cure, without question, the second and fourth infants.

When this patient was first admitted it showed besides the lesions already described, râles at both bases, especially on the left side, accompanied with a temperature that varied daily anywhere from 37.8 to 40.1 C. May 15 there was a definite and marked impairment of resonance of the left lower lobe, accompanied by bronchial breathing so that we could make a diagnosis of pseudolobar pneumonia. As a result of

this pneumonia, the infant did not make a complete change for the better until May 20. The presence of the pneumonia, however, did not obscure the definite and marked improvement in the scorbutic symptoms after the beginning of the malt soup therapy.

As stated above, May 11 the child received its first malt soup extract, and May 13 there could be seen a marked improvement in the joint sensitiveness. As a matter of fact, some improvement was noted May 12, twenty-four hours after the beginning of the therapy. May 14 a marked increase in urinary excretion was also noted, but inasmuch as the fluid intake was low, owing to the poor appetite of the child and its resistance to gavage, the increased urination may have been due more to the increased intake rather than to any diuretic effect of the malt soup extract, although, in all probability, the latter was a factor when one considers that the other children did take more fluid before they received their malt soup extract in the form of Keller's soup and, nevertheless, showed a marked increase in urinary excretion. May 15 the brawny induration of the right ankle was entirely gone, the tenderness of the left knee was markedly diminished, and the child offered no complaint when the left knee and thigh were flexed on the abdomen. Only the right thigh, owing to the presence of the suppurating hematoma, was still protected by the infant against too marked a movement, but even this swelling of the right thigh had been reduced in size, and there was also a decided improvement in the general condition of the child. It became interested in things, and, even though it was still very sick with its pneumonia, it tried to smile and would watch objects that were placed before it, something which it had not done before.

On the next day, May 16, the right thigh had reduced in size enormously and the baby was much more improved, as far as its general disposition was concerned; it smiled and the knees could be flexed without causing any pain. The same was true of the ankles. The pneumonia was still causing a rise of temperature up to 39.5 C., giving beautiful proof that the improvement was due to something different than a change in the condition of the lungs, which clinically could not be recognized. To our great surprise and amazement it was learned from the history that this infant had received nothing but its mother's breast-milk. No oranges, tomatoes, potatoes or any other foodstuffs were given it. The mother herself was well, had had no bleeding gums, no painful extremities, and had been eating a general diet, including potatoes. This child was the result of the sixth pregnancy, the first two having ended at six months, while the third, fourth, and fifth went to full term and brought forth infants who are living and well.

We appreciate fully that this history raises a justified doubt as to whether the symptoms in this child were due to scurvy. And yet, after considering the physical findings and the type and course of improvement in the picture after the giving of the malt soup extract, on the one hand, and, on the other, the great improbability that under the same treatment such a marked and rapid change in the condition of the extremities could have occurred if the lesions were due solely to some sort of an infection—we cannot come to any other conclusion than that this case is one of the rare cases of scurvy in breast-fed infants. Possibly when the etiology and the pathogenesis of scurvy will have been clearly established cases such as this one will appear less enigmatic.

So this last patient is also put down as a severe case of scurvy cured in its acute stage by the administration of malt soup extract in a dose of 100 gm. per twenty-four hours, making a total of at least three cases of severe and unquestionable scurvy, cured by the administration of malt soup extract.[2]

As stated before, Keller's malt soup is a food that is very prone to cause scurvy in infants, and yet there can be no question as to its curative effect in three of the above described cases, an effect that can be dissociated in these severe and yet rapidly cured cases from the quantity of the milk, the heating factor and the ageing factor, as all of these detrimental factors existed in each of the three cases of cure, as the following data will show:

The only factor, besides the malt soup extract itself, that might be considered as having been responsible for the improvement is the quality of the milk, for certified milk was used in the preparation of each batch of food, and it might be imagined that cows producing certified milk are possibly given a diet that would put into the milk more anti-scorbutic substances than would be found in the milk of the ordinary milk cows, which most likely has been used, as a rule, in the making of Keller's soup.

However, neither the fact that certified milk was used, nor the possibility of a greater anti-scorbutic content of such a milk make this idea seem at all probable, as the certified milk used in making the curative Keller's soup for infants came from the same certified dairy from which is obtained the certified skimmed milk which is used in the manufacture of S. M. A. milk, a food which will cause scurvy, even though it contains the same amount of milk as Keller's soup, if no anti-scorbutic is given in addition. And, finally, the food which the cows at the certified farm received was dry and varied in its source, as one would

2. The malt soup extract used in this work was labeled 8149 by the Borcherdt Company.

have expected from the fact that the one infant was fed from Sept. 27 to Oct. 12, 1918; the other from Jan. 2 to Jan. 18, 1919; and the third from May 10 to May 26, 1919. So it would be a strange coincidence indeed that cows fed at such widely separate periods on dry food-stuffs, known to have come from different sources, should produce a milk of such high antiscorbutic power that even in the quantity of not more than 330 c.c. for twenty-four hours, boiled, pasteurized, or even sterilized under pressure, and from two to three weeks old, would produce results so paradox to the universal proscorbutic experience with Keller's soup. Therefore, it would seem much more rational to assume that the one and the same batch of malt soup extract which was used in the case of each of these infants was, in all probability, responsible for the good therapeutic results.

The second infant received Keller's soup which was made with certified milk in the ordinary way by boiling, and which then, in addition, was sterilized under pressure for thirty minutes. The entire batch consisted of thirty-two quarts, and for seventeen consecutive days the patient received exactly the same food, making the last quart eighteen days old.

It may be interesting to note in this connection that the remainder of this lot of Keller's soup which cured this infant of its scurvy, produced a fatal scurvy in a number of guinea-pigs, even though their stools were normal during the earlier half of the experiment and decidedly diarrheic during the latter half, and even though they ate more than enough to meet their caloric and fluid requirements. At the necropsy most of these pigs had their large intestines one-half to two-thirds full of a soft, thin stool.

The fourth infant received Keller's soup, all of which was also made at one time, and the last quart of which was fourteen days old when consumed. This batch of food, however, was not subjected to sterilization under pressure.

Evidently, all of these factors were not adequate to reduce the curative properties of the malt soup extract to a level below immediate and marked therapeutic efficacy.

No conclusive facts regarding the cause of the presence of the antiscorbutic properties of malt soup extract No. 8149 can be given at this time. In the light of our present knowledge, however, there can be only one explanation, as a visit to the factory and a conference with the manufacturer of the malt soup extract convinced me that lot 8149 was alkalinized in the prescribed manner with methyl red as the indicator.

The most probable explanation would seem to us to be that the barley from which the malt used for the manufacture of the malt

soup extract was derived, had reached an age and stage of germination at which much antiscorbutic substance was produced, or that the barley grain itself possessed an unusually high amount of potential antiscorbutic material.

Valentin Fürst[3] called attention to the fact that while plain barley, oats, peas, etc., have none or not sufficient antiscorbutic powers to prevent the development of scurvy in guinea-pigs, the very same barley, oats, peas, etc., when brought to germination by being kept in a moist warm room for about three days, develop marked and adequate antiscorbutic properties, as tested out on guinea-pigs, and recently in the Chemical Abstracts (April 10, 1919) H. S. Paine[4] reports that E. Weill, G. Mouriquard and Mlle. Peronnet have found that cereal grains of ten days germination age have a greater antiscorbutic value than those of three days old.

If this is the true explanation of the presence of the antiscorbutic factor in the malt soup extract, then it should be possible to use in the manufacture of malt soup extract only malt that has been made from barley of the proper age and state of germination. This would be an addition to our present list of antiscorbutics of another agent of real value as malt soup extract can be used to advantage in other respects in the diets of infants and young children, especially of those that are inclined to be constipated.

The difference in therapeutic results between infants, on the one hand, and guinea-pigs, on the other hand, is undoubtedly due to the decidedly larger antiscorbutic requirements of the guinea-pigs.[5] From the work of Chick, Hume, Skelton [6] we know that a guinea-pig of about 250 gm. weight requires from 80 to 100 c.c. of raw milk daily to prevent the development of scurvy or, at least, to postpone its appearance for a long time, and according to Hess [7] the infant requires about 500 c.c. of raw milk in twenty-four hours. Such infants will weigh on an average at least 5,000 gm.; in other words, twenty times as much as a guinea-pig, and yet infants require only five times as much milk as do guinea-pigs to protect them against the development of scurvy.

3. Fürst, Valentin: Weitere Beiträge zur Aetiologie des experimentellen Skorbuts des Meerschweinchens, Ztschr. Hyg. u. Infekt. Krankh. **72**:132, 1912.

4. Paine, H. S.: Chemical Abstracts **13**:749 (April 10) 1919. Appearance of an Antiscorbutic Substance During Germination of Cereals. E. Weill, G. Mouriquard, and Mlle. Peronnet, Compt. rend. soc. biol. **81**:607, 1918.

5. Chick, H., Hume, H., and Skelton, R.: Antiscorbutic Principles in Limes and Lemons, Lancet **2**:735 (Nov. 30) 1918 .

6. Chick, H., Hume, H., and Skelton, R.: Antiscorbutic Value of Milk in Infant Feeding, Lancet **1**:1 (Jan. 5) 1918.

7. Hess, A. F., and Unger, L. J.: Factors Affecting the Antiscorbutic Value of Foods, Am J. Dis. Child. **17**:239 (April) 1919.

This experience with the guinea-pigs and infants fed with the same Keller's soup would indicate that the antiscorbutic content of the malt soup extract was relatively not as great as that of orange juice or tomato juice, although it was evidently sufficient to cure severe acute cases of scurvy in infants, and it may well be possible that a malt soup extract could be manufactured whose antiscorbutic powers would be distinctly greater than those present in the lots used for this work.[8]

CONCLUSIONS

1. A report is made of a rapid and marked cure, such as is experienced with orange juice, of three cases of severe infantile scurvy by the administration of 100 gm. of malt soup extract. In two of these the malt soup extract was given in the form of Keller's soup, in the third, in conjunction with S. M. A.

2. The explanation offered for the presence of the antiscorbutic property in this No. 8,149 lot of malt soup extract is that it was, in all

---

8. Since this article was submitted, the remainder of lot 8,149 was given to three infants, two of whom had clear-cut cases of scurvy, while the other never got beyond what at most could be called a subacute form. The data obtained were inconclusive and consequently are of no value. In the last mentioned child, seen during September, 1919, an otitis media, a pyelitis and a probable enteritis follicularis were responsible for the poor condition and the lack of improvement. The malt soup extract was given mainly together with S. M. A., but for five days it received it in the form of Keller's soup made with certified milk which came from the same farm that produced the milk used in the feedings for the cured cases presented in the article.

The first child had a clear-cut scurvy and came to the hospital during a severe hot spell in July, 1919, suffering in addition from a severe dyspepsia. The vomiting greatly limited the amount of malt soup extract retained and as signs of dehydration appeared the observation had to be stopped and the diet replaced by large doses of orange juice, barley water ad libidum and saline infusions with beneficial results.

The other child, 7 months old and weighing 7,000 gm., was seen in November, 1919, ill with a definite scurvy. It received the very last part of lot 8,149, which was just enough for four days. No definite improvement was registered at the end of this time. It was then given for four days 100 gm. of lot 9,322, neutralized with potassium carbonate, which had recently been made at the factory. This also was without beneficial result and so for the next five days 100 gm. of lot 9,322, to which, however, no potassium carbonate had been added at the factory, were administered, but again no betterment was observed. Thirty c.c. of orange juice were given four times per day and this brought good results. The symptoms, however, did not disappear as completely and as quickly as usual. It is possible that this child required an especially large amount of antiscorbutic to remain well, as the mother, who is intelligent and who seems dependable, states emphatically that the child got 1 teaspoonful of orange juice daily from his third month on and "did not need any more, because his bowels were all right." This child was fed since its second month on a simple dilution mixture at one of the local infant welfare stations.

probability, made from barley of the proper age and state of germination or from a lot of barley possessing an unusually.high amount of potential antiscorbutic material.

3. The suggestion is made that all malt soup extract could be manufactured from barley of an age and state of germination that would insure its large and adequate content of the antiscorbutic factor, and that in this manner another antiscorbutic, of value also in other respects to infants and children, could be added to the list of our regular and dependable antiscorbutics.

ANEURYSMS OF THE THORACIC AORTA IN CHILDREN

WITH REPORT OF TWO CASES *

JOSEPH K. CALVIN, S.B., M.D.

CHICAGO

Aneurysm of the thoracic aorta is a rare condition in children. I have been able to collect and review thirty-one cases from the literature, besides the two cases which I have to report.

ETIOLOGY

There is a great diversity of opinion on this subject, mainly because the real causative factors have not been worked out in many cases. Some authors believe that syphilis is practically always the prime factor in children as in adults, but a careful study of the available cases does not confirm this view. Bronson [1] has grouped these cases according to the etiologic factors into: (1) those aneurysms due to atheromatous degeneration; (2) those resulting from trauma (rare); (3) those due to erosion of the aorta from without; (4) a few following congenital malformations, and (5) last, but probably the most important factor in childhood, aortic aneurysms following in the wake of acute infectious diseases. Osler remarks that in adults the specific fevers commonly cause areas of degeneration in the intima of the aorta and occasionally in the media. Klotz [2] has shown that in childhood the aorta may be attacked during an acute infectious disease, especially those due to the streptococci. He claims that the organisms gain entrance to the aortic wall through the vaso vasorum and lodge in the media, causing degenerative changes which lead to a gradual weakening of the wall, with resulting dilatation, fibrosis and possibly aneurysm.

A summary follows of the cases in which the apparent determining cause was an acute infectious aortitis.

CASES DUE TO ACUTE INFECTIOUS AORTITIS

CASE 1.—A definite history of five severe attacks of chorea was given. During the third attack the heart was involved. This attack was followed by diphtheria. During the fifth attack the aneurysm was diagnosed, five years

after the initial chorea. The blood Wassermann was negative. There were no signs of congenital syphilis, nor any family history of syphilis. Three other children, one older and two younger, were well.

CASE 2.—This patient developed symptoms of "heart trouble" after an operation for appendicitis, with a postoperative pneumonia, which in turn was followed by arthritis. Two weeks after this acute arthritis, palpitation of the heart began, confining him to bed for six months. He had had nine previous attacks of acute arthritis which lasted for a week at a time. Two negative blood Wassermanns were obtained; one at Michael Reese Hospital and the other at Cook County Hospital, the interval between the tests being five months. No signs of congenital syphilis were present. The mother and father both died of pneumonia. One sister died from an unknown cause.

REVIEW OF LITERATURE

MacNalty[3] reports that his patient had scarlet fever at the age of 4 years, measles at 5 and pharyngitis and cough at 8, followed by heart symptoms which persisted off and on. The aneurysm was diagnosed six years after the onset of the heart symptoms. The child had a cleft palate and hare lip, but no signs of syphilis. There was no family history of syphilis, although the father had heart disease.

Klotz[2] reports that his patient had arthritis six months before, following which heart symptoms developed and "heart disease" was diagnosed. Then shortly before death he developed another acute arthritis and endocarditis. Positive blood cultures of pure streptococci were obtained. Sections through the aneurysm at necropsy revealed acute inflammation, and streptococci were found in these tissues. No evidence of syphilis was revealed.

Roy[3a] believes his case was caused by an acute infection of some kind, but admits that the cause is unknown. There was no history nor evidence of syphilis.

Jordan[4] reports a history of rheumatism with possible septic aortitis in his case. No history nor evidence of syphilis was revealed.

Thieberge's[5] patient had an acute endocarditis four months before the aneurysm was diagnosed. The family history was negative. There were no evidences of syphilis.

A. A. Smith's[6] patient had acute arthritis one year before the aneurysm was diagnosed.

Bacelli's[7] patient had two attacks of acute articular rheumatism. One was two years before, and the other six months before the aneurysm was diagnosed. There was no clinical evidence of syphilis. The family history was negative.

3. MacNalty, A. S.: Proc. Roy. Med. Soc., London **10**:35 (Clin. Sec.) 1909.
3 a. Moizard and Roy: Ann. de méd. et chir. inf. **12**:149, 1908.
4. Jordan, A. C.: Lancet **1**:515, 1903.
5. Thibierge: La France méd. **2**:913, 1881.
6. Smith, A. A.: Med. Rec. **44**:349, 1893.
7. Bacelli, G.: Semaine méd. **18**:137, 1898.

Le Boutillier's [8] patient gave a history of two attacks of pertussis, the first when 9 days old, the other at the age of 3 years, and arthritis at 4 years, at which time some heart trouble was diagnosed. Typhoid developed at 7 and measles at 9. The aneurysm was diagnosed at 9. No physical evidence of syphilis was present. One child died of pertussis. Otherwise, the family history was negative.

CASES DUE TO SYPHILIS

A summary of the cases in which the apparent determining cause was syphilis is interesting.

Heiman [9] reports the case of a woman and her boy who had a four plus blood Wassermann reaction. The mother had had two miscarriages and the father died of epilepsy. The child had several attacks of acute articular rheumatism, the last one about two years before the aneurysm was diagnosed. The child had an enormous spleen and a tumor of the liver which was assumed to be a gumma.

Willson [10] reports a case in which the father had a chancre, saddle nose and developed epilepsy at 21. The mother was healthy and showed no evidence nor history of syphilis. A congenital heart lesion was diagnosed in the child at 6 weeks of age and the aneurysm was found at 4 years.

A study of the aortas of still-born infants often reveals mononuclear infiltration about the vessels of the media, spirochaetes and early degenerative changes. Thus, we can easily realize how such changes may give rise to aneurysms later in life in congenital syphilitics.

CASES DUE TO TRAUMA

Cases apparently due to trauma are rare.

In McKeen's case [11] the symptoms followed severe trauma to the chest six months before the aneurysm was diagnosed. Pendin [12] also believed that his case followed a trauma.

CASES DUE TO EROSION

A summary of those cases apparently due to erosion from without follows:

8. Le Boutillier, T.: Case of Aneurysm of Transverse Portion of Aortic Arch, with a Table of Reported Cases Under Twenty Years of Age, Am. J. M. Sc. **125**:778, 1903.

9. Heiman, H.: Aneurysm of Ascending Arch of Aorta in a Boy of Thirteen, Arch. Pediat. **36**:543 (Oct.) 1919.

10. Willson, R., and Marcy, A.: Proc. Path. Soc. Phila. **16**:63, 1914.

11. MacKeen, R. A. H.: Med. News **61**:272, 1892.

12. Pendin, A.: Ein Fall von Aneurysm Aortae Ascendenti bei einem 12 jährigen Mädschen, St. Petersburg med. Wchnschr. **7**:195, 1890.

Hutchinson [13] reports that in his case the aorta was healthy to the edges of the aneurysm, which appeared to be a caseous gland ruptured into aorta.

In Smith and Targett's [14] case the posterior mediastinum was matted together with inflammatory products, and the aorta had been eroded from without.

Willett [15] showed that in his case the aneurysm was due to the discharge of a suppurating lymph gland into the aorta.

Jackson Clarke described two cases in which aneurysm was due to ruptured caseous lymph glands.

CASES DUE TO CONGENITAL MALFORMATION OF AORTA

A number of authentic cases have been recorded of a thoracic aortic aneurysm resulting from congenital malformation of the aorta.

Bronson and Sutherland [1] report a case in which the aorta was stenosed in the ascending portion, proximal to which was an aneurysm. There was no history or evidence of syphilis; the Wasserman was negative; no spirochetes nor aortitis were found. There had been no acute illnesses. The family history was negative.

In Wasajerna's case a nearly complete congenital stricture was present in the ascending aorta with an aneurysm just proximal to it.

In Smith and Targett's case the aneurysm was distal to a congenital stenosis.

In Armitage's case a congenital heart lesion was present. The aneurysm was diagnosed at 7 years of age.

The symptoms of two cases appeared suddenly following an acute exertion. In these cases aneurysm had not been diagnosed until the appearance of the acute terminal symptoms.

PREDISPOSING CAUSES

Age.—Twenty-one cases occurred under 12 years, and twelve cases between 12 and 18 years. At 2, one case occurred; at 3, one case; at 4, five cases; at 5, three cases; at 6, two cases; at 7, one case; at 9, four cases; at 10, one case; at 11, one case; at 12, three cases; at 13, three cases; at 14, two cases; at 15, three cases; at 16, one case; at 17, two cases; at 18, two cases.

Sex.—Twenty patients were boys, and ten were girls.

13. Hutchinson: Tr. Path. Soc. London **5**:104, 1854.

14. Smith, F. J.: Aneurysm of Aorta in a Boy of Nine Years, Tr. Path. Soc. Lond. **48**:53, 1897.

15. Willett, E.: Aneurysm of Aorta in Child of Four Years, Tr. Path. Soc. Lond. **43**:38, 1892.

16. Wasajerna, E.: Ein Fall von Aortaruptur nach Schlittschuhlaufen, Ztschr. f. klin. med. **90**:405, 1903.

Heart.—The heart was normal in nine cases. It was hypertrophied in ten cases, in all but two of which valvular lesions were present. The aortic valve was diseased in twelve cases. The mitral valve was diseased in eight cases. The tricuspid valve was involved in one case.

Thus, as far as the heart was concerned, hypertrophy alone was present in two cases; hypertrophy with only the aortic valve involved was present in two cases; hypertrophy with both the aortic and mitral valve involved was present in six cases; hypertrophy with only the mitral involved was present in one case; aortic and mitral involvement without mention of hypertrophy was present in one case; and aortic valve involvement without mention of hypertrophy was present in four cases.

Aorta Apart from the Aneurysm.—In seven cases the aorta was normal; in six cases atheroma was found; in two cases there was an acute septic aortitis, and in three cases stenosis of the aorta near the aneurysm was present.

Pathology of the Aneurysm.—The aneurysm was located in the ascending arch in twenty cases; in the descending arch in two cases, and in the transverse arch in five cases.

Sac.—The description of the sac is mentioned in relatively few of the cases.

In Willett's case [15] the opening was irregular and small and the walls in places were as thick as the aorta. Microscopically, it appeared like an old blood clot with an attempt at a lining membrane. He considered that it might have been a ductus arteriosus remaining open at its distal end, or the remains of a large lymph gland with its contents discharged into the aorta. The heart was normal.

In R. T. Smith's case,[17] an aneurysm the size of a walnut had ruptured into the pericardium. The heart showed mitral disease and the aorta showed atheroma.

In Hutchinson's case,[13] the aneurysm was the size of two chestnuts. The heart and vessels were normal.

In Sanne's case,[18] the sac was the size of a small nut. The heart showed aortic valve involvement, and the aorta showed atheromas.

In Bronson and Sutherland's case [1] a fusiform aneurysm the size of the heart was present in the ascending arch. The walls were 3 mm. thick. All the valves were normal, as was the myocardium, although the left ventricle was hypertrophied. The aorta was stenosed between the ductus arteriosus and the left subclavian artery. Microscopically, the thickening of the walls was due to hyalin sclerosis affecting the

17. Smith, R. T.: Lancet **1**:626, 1834.
18. Sanné: Rev. méns. d. mal. de l'enf. **5**:56, 1887.

deep intima and underlying media. The cells were few and of the connective tissue type. No bacteria, or spirochetes or evidences of aortitis were found.

In Klotz's case [2] a saccular aneurysm the size of a pigeon's egg was located in the ascending aorta. The heart was hypertrophied, the mitral and aortic vales were involved and a septic aortitis was present. Infarcts were present in various organs. Microscopically, the tissues of the heart valves and ascending aorta were infiltrated with polymorphonuclears and other evidences of acute inflammation. Streptococci were found in these tissues and in the blood.

The roentgen-ray is of great aid in determining gross pathologic features during life, but has only been used in Bronson's, Heiman's and my own cases as far as can be ascertained. The electrocardiograph also is of marked help in determining the condition of the heart during life. It was employed in Heiman's and in my cases.

SYMPTOMS

Many of the symptoms were those due to the accompanying heart lesion with decompensation.

Symptoms.—In those cases in which symptoms referable to the aneurysm are mentioned, the onset was sudden in five cases (during exertion) and gradual in the rest. Dyspnea was present in twelve cases. Cough was present in seven cases, although no particular variety was described. Precordial pain was present in six cases and palpitation in five.

Physical Findings.—Only the physical findings referable to the aneurysm are noted. A systolic murmur, loud and harsh over the base and transmitted up into the vessels, was present in nineteen cases. This was accompanied by a softer diastolic murmur when aortic regurgitation was also present. Increased dullness over the aortic arch area was present in thirteen cases. A systolic thrill over the base and great vessel area occurred in ten cases. Expansile pulsation of an abnormal tumor in the neck (suprasternal fossa) occurred in eight cases. One radial pulse was slowed in five cases and a tracheal tug was noted in one case.

The blood pressure in the four cases in which it was noted was 170 mm. of Hg, 140 (syphilitic case), 135 and 125, respectively.

The electrocardiograph in Heiman's case showed a left ventricular predominance, the notching of R in Lead II and the inversion of T in all three leads. In my case, the findings are noted in the report of the case.

Duration.—The duration from the beginning of symptoms was from three days to eight years. In those cases where the duration was

noted it was as follows: three days, ten days (2 cases), two months, three months, six months (3 cases), two years, three years, four years (2 cases), six years, seven years and eight years, respectively.

Causes of Death.—The causes of death were: Rupture into the pericardium, eight cases; acute endocarditis, three cases; acute pericarditis, two cases; asphyxia, two cases; cardiac decompensation, two cases; pneumonia, two cases; smallpox, one case; tuberculous meningitis, one case.

REPORT OF CASES

CASE 1.—*History.*—R. M., a schoolboy, aged 11, entered the Cook County Hospital, June 17, 1919. Three years previously, four weeks after surviving an appendectomy and postoperative pneumonia, the patient developed polyarthritis. Two weeks later, heart symptoms developed which confined him to bed for six months, after which he was able to do light work. Pain in the precordium was present for the nine months preceding his entrance to the hospital. This pain was continuous, with severe exacerbations, causing him to cry, lie down and grit his teeth. At other times, the pain was of a dull aching character and did not keep him awake at night. It was located in the precordium, especially to the left of the midline, but did not radiate. For the previous month, he had pains and itching in the palms and soles. Dyspnea was present on exertion, but was not marked. Otherwise the boy was in good shape, felt well and had no other symptoms.

His previous illnesses, besides those immediately antedating his "heart trouble," were nine previous attacks of acute arthritis, usually involving the knees and confining him to bed for about one week at a time. No such attack had been present for the past three years. He developed influenza in the fall of 1918, but was in bed only five days. The patient had chickenpox and pertussis when very young.

Family History.—The father was a soldier and died of pneumonia nine years ago. The mother died of influenza in 1918. One sister died of unknown cause. No heart disease existed in the family.

Physical Examination.—Patient was a well nourished boy, about 11 years old, not acutely ill, and walked into the hospital. The pupils were equal and regular, reacting well to light and accommodation. The tonsils were hypertrophic, but contained no pus nor caseous plugs and were not reddened. Two carious teeth were present but no root abscesses.

The radial pulse was equal on both sides, 100 per minute when sitting at rest, regular and distinctly of a very forcible water-hammer type. A capillary pulse was present (seen on lips and fingernail beds). The large peripheral arteries pulsated visibly and forcibly, i. e., the carotids, brachials and dorsal pedals. A pistol shot tone could be heard over the femoral artery with a to and fro murmur.

CHEST: *Inspection* of the chest revealed a regular easy type of respiration, 24 per minute while sitting at rest. The chest was symmetrical and normally formed; no bulging was present and both sides were equal at the nipple line. The circumference at this level was 28 inches at rest, 29 inches during inspiration and 27.5 inches after expiration. A diffuse heaving pulsation was present over the precordium, especially localized at the apex in the sixth interspace at the midaxillary line. A violent throbbing was present in the suprasternal region and carotids.

Palpation confirmed the above findings. A systolic thrill was felt over the aortic area, becoming more pronounced toward the neck. No thrill was present over the apex. *A dome-shaped semiglobular mass was felt projecting upward from the suprasternal notch,* more to the right than to the left. This mass

had a violent expansile pulsation with a marked thrill and bruit. The mass measured 7.5 cm. wide, extended 4 cm. up into the neck at the height of pulsation and 3 cm. at the rebound. Its pulsation was synchronous with that of the heart. A tracheal tug was present.

Percussion revealed the following areas of dulness: At the first interspace, 4 cm. to the right and 4 cm. to the left of the midsternal line; at the second interspace: 4 cm. to the right and 5 cm. to the left of the midsternal line; at the nipple level: 4.5 cm. to the right and 12 cm. to the left of the midsternal line. The greatest transverse diameter is at the sixth interspace, 7 cm. below the nipple line: 4 cm. to the right and 14 cm. to the left of the midsternal line. The greatest oblique diameter is from the second rib to the sixth interspace, and measures 21 cm.
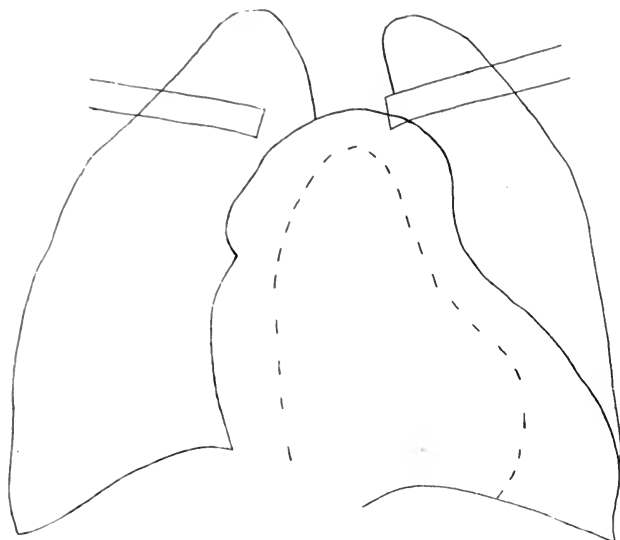
Fig. 1.—Case 1. Orthodiagram of heart, aortic arch and lungs, showing the aneurysmal dilatation of ascending portion and arch of aorta, and the enlarged heart. - - - - - represents the outline of about the normal sized heart and aortic arch in a child of this weight and age. Orthodiagram made by Dr. E. Blaine during fluoroscopic examination.

Auscultation reveals a loud, harsh, rasping to-and-fro systolic-diastolic murmur, heard all along the sternum, best to the left of the sternum over the third costochondral junction, and transmitted up toward the bulging in the neck where it is mainly systolic (very loud and rough), and down toward the apex it diminishes rapidly in intensity. About half way toward the apex there begins a presystolic-systolic murmur, which becomes quite loud at the apex, but not as loud, however, as the first murmur is over the aortic area.

ABDOMEN: The abdomen is negative, except for tenderness of the appendix scar; and the liver is palpable one and one-half fingers below the costal margin. Marked epigastric pulsation, synchronous with the heart beat, is seen.

The finger nails are slightly cyanotic, and slight clubbing of the fingers is present. The reflexes are normal

Blood Pressure.—The blood pressure readings were as follows: June 19: Right arm, systolic 140, diastolic 30; pulse pressure, 110. Left arm, systolic 135,

diastolic 25; pulse pressure, 110. June 30: Right arm, systolic 132, diastolic 10. Left arm, systolic 120, diastolic 10. .

Laboratory Examinations. — The blood Wassermann was negative at two reliable hospital laboratories on two successive occasions at an interval of six months. The lipoid, cholesterinized and straight Wassermann tests were all negative. The urine was repeatedly negative. The blood picture showed 4,800,000 erythrocytes, 80 per cent. hemoglobin, 14,000 leukocytes, of which 15 per cent. were small mononuclears, 5 per cent. large mononuclears, 78 per cent. polymorphonuclear neutrophils, and 2 per cent. eosinophils.

Course.—At first, the patient complained greatly of precordial pain and burning sensations in the hands and feet. The temperature was 98.2 F.; pulse 96, and respiration, 20. Rest in bed and moderate doses of digitalis were administered. By the end of fifteen days these symptoms had gradually diminished and disappeared. At that time the patient felt very comfortable. Temperature, 98 F.; pulse, 100; respiration, 22. He was then allowed up in a
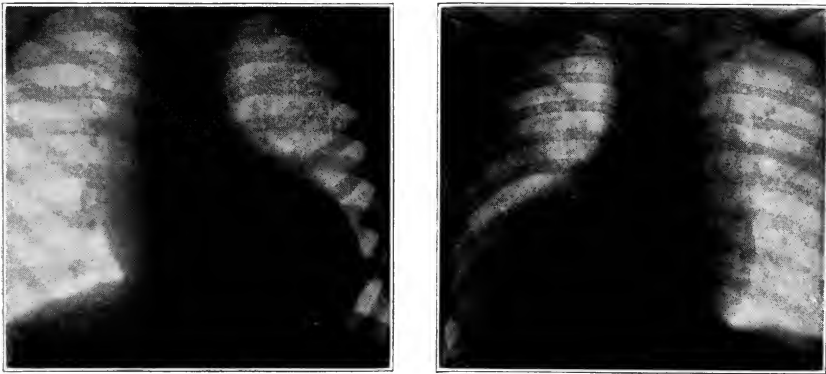
Figs. 2 and 3.—Roentgenograms, anterior and posterior view. The heart is of the aortic valve lesion type with a large left ventricle and increased right auricle. The aortic shadow is very greatly increased, and this shadow increase extends into the base of the neck. This condition is an aneurysmal dilatation of the ascending portion and arch of the aorta.

wheel chair. A month after admittance, he was up and about and the digitalis was discontinued. The patient has been feeling well since.

CASE 2.—*History.*—G. H., a Jewish school girl, aged 9, entered Michael Reese Hospital, March 15, 1908. She had been in good health until 4 years of age, when she developed chorea, which was very severe, lasting six weeks. Her heart was not affected. She remained well for eight months and then developed a second attack of chorea, lasting six weeks, not as severe as the first, and not involving the heart. Nine months later, a third attack of chorea developed, complicated by diphtheria. Her heart was "weak" at this time. Ten months later a fourth mild chorea occurred, lasting three weeks and definitely affecting her heart (according to physician in attendance at that time). She remained well for eighteen months, and then the attack began which brought her to the hospital. The worst of the condition was over after two weeks in bed at home. The patient walked to the hospital and had a typical chorea minor. Dyspnea on exertion was present at this time.

Previous Illness.—She had had measles at 3 years. She had never had arthritis, "rheumatism" or scarlet fever.
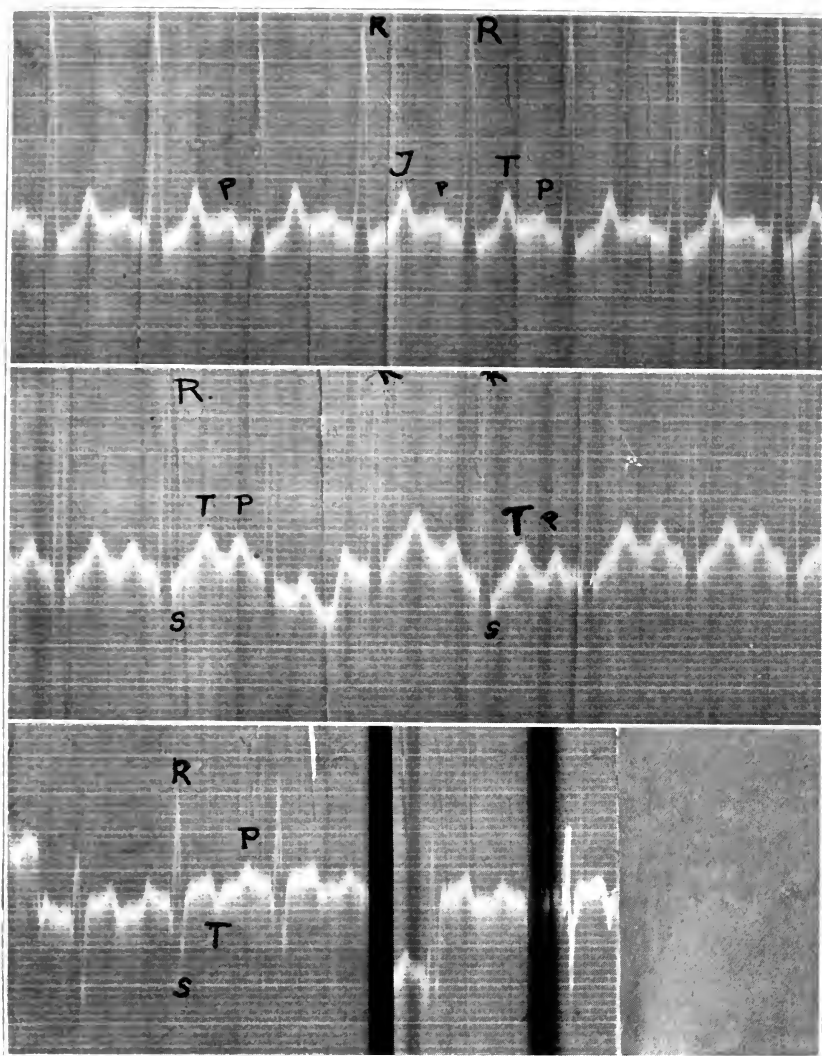
Fig. 4.—Case 1. Electrocardiogram, Leads I, II and III show a pronounced left preponderance, as shown by the high R in Leads I and II and the S of Lead III. Evidence of aortic disease is shown by the very great height of R in Lead II. There is an isolated premature contraction in Lead II (auricular in origin). The T is inverted in Lead III (of no pathologic significance). The P in Leads I and III is wide and notched, a finding in mitral stenosis. P-R 0.16 second; rate 199.

Family History. — There was no family history of heart trouble. Both parents were living and well. One older child and two younger children were well. None had had chorea.

Physical Examination.—The patient was a rather delicate looking little girl, small for her age, with sallow complexion, apathetic dull look and appearing to be rather weak. The pupils reacted to light and accommodation. The lips showed a capillary pulse plainly. There was a marked visible pulsation of the jugulars and carotids, and over the latter a marked thrill and systolic murmur. In the suprasternal notch, a tumor showing expansile pulsations, synchronous with the heart beat, was plainly seen. A distinct thrill was felt, and a systolic-diastolic murmur heard over it. There was a slight kyphosis and a hollow chest. The expansion of the chest was small but equal on both sides. A moderate right sided scoliosis was present. The lungs were negative.

Heart.—The right border was just beyond the right sternal margin; the apex was 2.5 cm. beyond the nipple line and in the sixth interspase. The upper border was at the third rib. The apex beat was diffuse. An oval shaped area of dulness was present behind the manubrium sterni, the apex of which
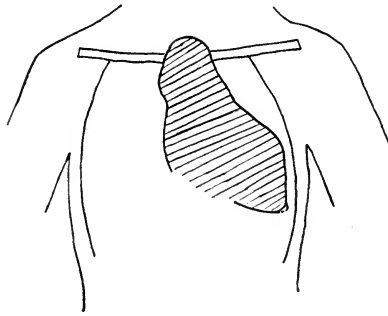
Fig. 5.—Case 2. The shaded portion represents the area of cardiac and aortic arch dulness as determined by percussion and palpation.

was just above the suprasternal notch, extending laterally beyond the margins of the manubrium, and merging into the base of the heart below. At the apex a low pitched, booming, systolic and diastolic murmur was heard, the systolic being stronger. Over the aortic area a rough, loud systolic and a soft blowing diastolic was heard loudest over the third intercostal space to the left of the sternum and transmitted up into the neck and down along the sternum. A visible pulsation was present in all the peripheral arteries. The right radial pulse was smaller in volume and tension than the left.

Blood Pressure.—March 17: Right systolic, 115; left systolic, 125. March 23: Right, 115; left, 125. May 5: Right, 135; left, 135.

Laboratory Findings.—The stools and the urine were negative. The blood Wassermann was negative. The blood examination revealed a secondary anemia: erthrocytes, 3,848,000; hemoglobin, 62 per cent.; leukocytes, 7,200, of which 5 per cent. were small mononuclears, 26 per cent. were large mononuclears, 68 per cent. polymorphonuclears, and 1 per cent. were eosinophils.

Diagnosis.—Chorea; secondary anemia; thoracic aortic aneurysm; chronic endocarditis with hypertrophy of heart.

Course and Treatment.—The usual treatment for chorea and anemia was instituted. The patient responded well and left the hospital in three months. Six months later she returned with symptoms of cardiac decompensation. After

four months in the hospital she felt well enough to return home. She returned again two months later with symptoms of cardiac decompensation. This time she did not respond to treatment, and died one month later. A necropsy was not obtained.[19]

19. The following references may also be consulted:

Berry, S. H.: Brit. M. J. **2**:1745, 1898.

Horder, T. J.: St. Bartholomew's Hosp. Rep., London, 1908.

Koos, A.: Aneurysms in Childhood, Arvos' hetil, Budapest **56**:398, 1912.

McGraw, T. A.: Aneurysms in Young People, Tr. Am. Surg. Assn. **27**:532, 1909 (Armitage and Keen report of cases in this article also).

Miquel: Bull. gén. de thérap. **9**:393.

Moore, N.: Tr. Path. Soc. Lond. **34**:71, 1882.

Moutard-Martin: Bull. de la soc. Anat., 1875, p. 775.

Murdock, B.: Edinburgh Hosp Rep. **6**:84, 1900.

Rie(s): Wien. med. Wchnschr. **39**:556, 1889.

Roger, M.: Bull. et mém. Soc. méd. d. hôp. de Par., 1863, p. 499.

Rotch, T.: Roentgen Ray in Pediatrics. Philadelphia, J. B. Lippincott Co., 1910, p. 140.

CONGENITAL MALFORMATIONS OF THE ESOPHAGUS

WITH REPORT OF TWO CASES *

R. P. REYNOLDS, M.D., AND W. W. MORRISON, M.D.

NEW YORK

Cases of congenital malformation of the esophagus are extremely rare, and many standard works on embryology, anatomy, pathology or pediatrics dismiss the subject with but a few words. In the large necropsy service of Bellevue Hospital, only one case has been recorded in the last sixteen years.[1]

The etiology of the condition still remains in doubt, although several theories to explain it have been brought forward. MacKenzie[2] holds it possible that injury to the ovum or spermatozoa before fertilization may cause the defect. Trauma to the mother or fetus, abnormalities of the placenta, hydramnios and diseases on one or the other parental side, especially syphilis, have all been brought forth as possibilities, but, as Kreuter[3] states, they are not worth serious discussion. Associated malformations are uncommon and most of the children recorded as having esophageal abnormalities were otherwise healthy at birth. Ballantyne[4] calls attention to the fact that the position of the imperforation is practically always at the level of the lower portion of the trachea, and that the gastric portion almost always opens into the trachea. The esophagus, bronchi and lungs all develop from the foregut. Klebs, as quoted by Kreuter, believes that at the common primordium of these structures there is an unequal division of the primitive tissue, the respiratory tree developing at the expense of the esophagus. Plausibility is lent to this theory as the anomaly most often occurs at the bifurcation of the trachea. It is at this point that the primordium for the respiratory organs arises from the foregut.

Krauss[5] believes that the partial obliteration of the esophagus is due to pressure atrophy caused by the primitive arterial vessels crossing

1. St. George, A. V.: Proc. N. Y. Path. Soc. **18**:32, 1918.

2. MacKenzie, M.: Diseases of Larynx and Esophagus, Philadelphia, Blakiston's Son & Co., 1884, p. 149.

3. Kreuter, E.: Deutsch. Ztschr. f. Chir. **79**:1, 1905.

4. Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene, New York, William Wood & Co. **2**:462, 1905.

5. Krauss, F.: Nothnagel's Special Pathology and Therapeutics, Vienna **16**:96, 1902.

the esophagus in an unusual manner during early fetal life.   Kreuter, who reviews all the etiologic possibilties, believes that the esophageal defect is due to arrest of development which means failure of the solid esophageal tube to open.   He states that the communication between the esophagus and bronchi is explainable from the standpoint of incomplete separation of the respiratory tract from the foregut. Keibel and Mall [6] state that to produce the common anomaly, the lower

ESOPHAGUS

ARCH OF
AORTA
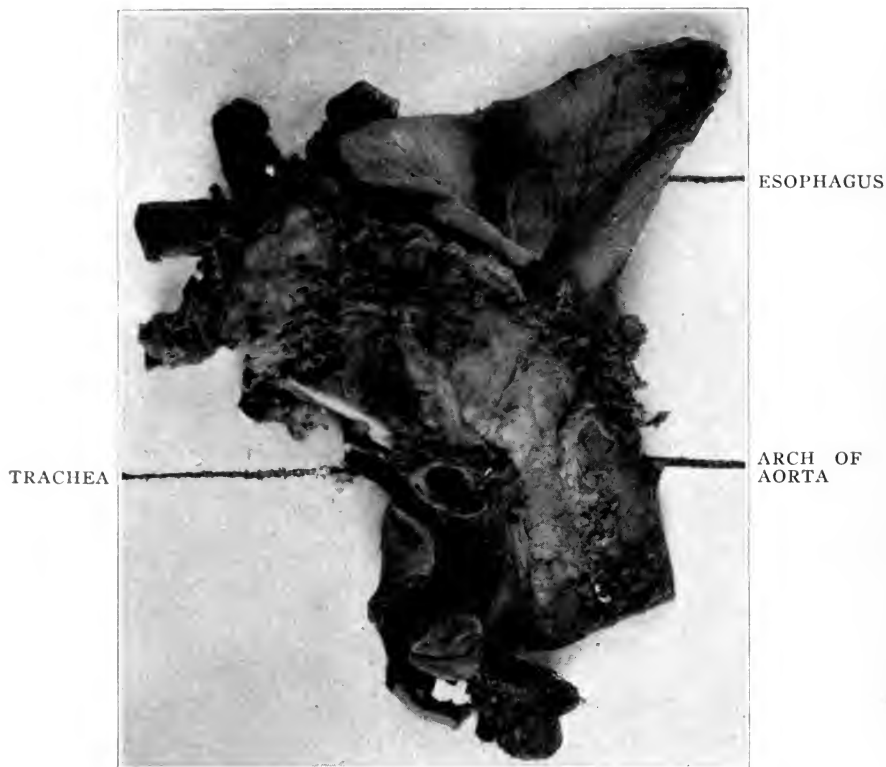
TRACHEA

Figure 1

portion of the trachea-esophageal septum must fail to develop, thus leaving the esophagus in communication with the lower part of the trachea.

In reviewing the literature of the subject, MacKenzie, in 1884, collected sixty-three cases.   In 1905, Kreuter, including those cases collected by MacKenzie, found 111 in all, and of this number ninety-eight were atresias and thirteen stenoses.   Plass,[7] in reviewing the

6. Keibel and Mall: Manual of Human Embryology, Philadelphia, J. B Lippincott Co. **2:** p. 313.

7. Plass: Johns Hopkins Hosp. Rep., 1919.

literature up to and including 1917, was able to find 204 reported cases. Since then Cautley,[8] Apfel,[9] Crowdy,[10] Huntington,[11] Kastner [12] and Shaw [13] have reported one case each, and Brenneman [14] four cases.

The clinical picture is quite definite and the diagnosis is comparatively simple. The child is apparently healthy and swallows liquid readily, but regurgitation occurs in from one to three minutes after swallowing. On taking food, the child becomes cyanotic, often coughs violently, makes gurgling noises, and the vomitus is foamy and alkaline

Figure 2

or amphoteric in reaction. These suffocative attacks are repeated on every attempt to take food. If the patient lives a few days, mechanical dilatation of the upper sac may occur and a few teaspoonfuls of

8. Cautley: Brit. J. Child. Dis. **14**:1, 1917.
9. Apfel: New York M. J. **108**:108, 1918.
10. Crowdy: J. M. Res. **38**:469, 1918.
11. Huntington et al.: Boston M. & S. J. **180**:354, 1919.
12. Kastner: Arch. Pediat. **37**:11, 1920.
13. Shaw: Am. J. Dis. Child. **20**:6, 1920.
14. Brenneman: Am. J. Dis. Child. **16**:143, 1918.

fluid may be retained, but as soon as the sac is full the reflex phenomena recur. A catheter passed into the esophagus under the fluoroscope makes the diagnosis certain.

In the matter of treatment, the only hope of saving the child is to perform gastrostomy as soon as the condition is diagnosed. The technic may be difficult, as the liver may be large and the stomach contracted, as in Case 1, in which there was no tracheo-esophageal fistula. On the other hand, where a tracheo-esophageal fistula is present, as in
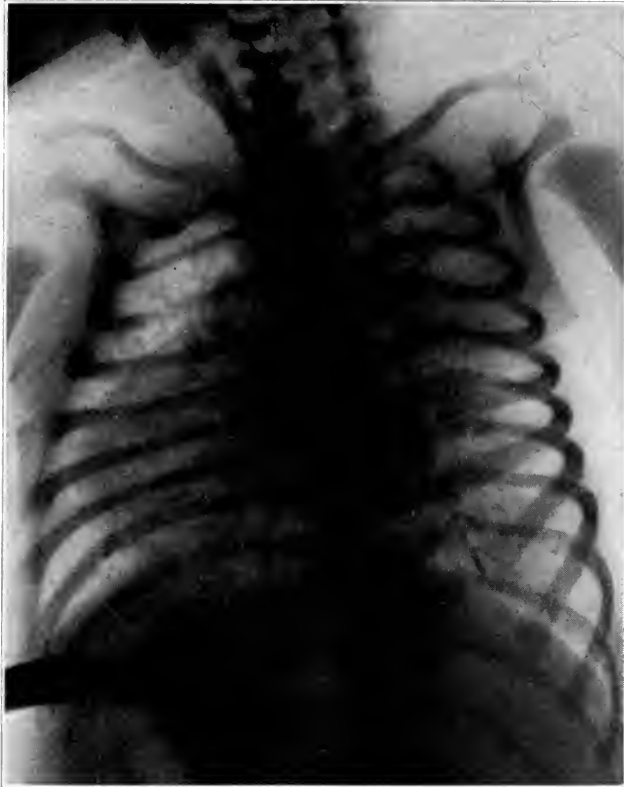
Figure 3

Case 2, the stomach may be ballooned out with gas. Even if the operation is successful, death may result from regurgitation of stomach contents through the tracheo-esophageal fistula into the lungs and there set up an aspiration pneumonia. Following the operation, in Case 2, dark brown fluid was vomited from the mouth; this was undoubtedly stomach contents which had been forced up through the tracheo-esophageal fistula into the trachea and then out through the mouth.

These congenital esophageal malformations have been classified by Whipham and Fagge [15] as follows:

A. Congenital absence of the whole esophagus, a very rare condition.

B. Bifurcation of the esophagus with junction of the two portions near the lower end, only one case reported.

C. (1) Congenital atresia in which the esophagus is divided into two parts, the least rare condition. The upper end terminates blindly in a more or less expanded culdesac. The lower end opens above into the trachea or one of the bronchi, and below in a normal manner into the stomach. The two segments of the gullet are connected by a fibrous or muscular cord.

(2) Much more rarely there is no opening of the lower part into the air passages, the two blind ends being merely jointed by a fibrous band.

D. Stricture caused by a fold of mucous membrane projecting into the lumen of the tube like a diaphragm (a) at the upper part of the esophagus immediately below the pharynx, and (b) near the lower end.

E. Congenital stenosis of the lower end of the esophagus.

Case 1 belongs in the above classification under Group C-2. It is one of the rarer forms of a rare condition. Case 2 belongs under Group C-1—one of the common forms.

REPORT OF CASES

CASE 1.—*History.*—A baby girl was born of an apparently healthy mother at the Bellevue School for Midwives. Five days later the child was admitted to the Children's Surgical Service of Bellevue Hospital with the diagnosis of hypertrophic stenosis of the pylorus, of the congenital variety. The diagnosis had been made because, without other symptoms, the child had vomited everything taken by mouth since birth. The child weighed about 6 pounds at birth. Regurgitation of fluid taken by mouth occurred within one to three minutes after swallowing. The vomitus was mixed with frothy mucoid material, and was amphoteric in reaction. Bowel movements had been regular and consisted entirely of meconium. Urination was normal.

Physical Examination.—The child was markedly undernourished, but otherwise seemed normal, except for the local condition. Examination revealed an apparently normal abdomen. There was the usual easily palpated liver, but no masses, no distention and no peristalsis were visible on prolonged observation. A soft rubber catheter was passed into the esophagus under the fluoroscope. There was no obstruction to its passage about 5 inches from the child's lips and the end of the catheter was seen to be stopped at a point opposite the fourth rib anteriorly, at the level of the transverse part of the arch of the aorta. A diagnosis of congenital atresia of the esophagus at the level of the fourth rib was made.

Surgical Treatment.—Although the outlook seemed hopeless, it was thought advisable to attempt to maintain the nutrition of the child by means of a simple gastrostomy. This was done by Dr. Doran under light ether anes-

---

15. Whipham, T. R. C., and Fagge, C. H.: Lancet **1**:22, 1905.

thesia in twenty-five minutes. A No. 16 soft rubber catheter was inserted into the stomach through its anterior wall. Two purse-string sutures with inversion held the catheter in place. The catheter was brought out through the left rectus in a stab wound made for the purpose. The stomach at the site of the gastrostomy was anchored to the parietes. There was no evidence of pyloric stenosis. The child was considerably shocked and was given stimulation, but died in about three hours.

Abbreviated Necropsy Protocol. — The body was that of a white female infant, 5 days old, 50 cm. in length, weighing about 6 pounds. Rigor mortis was absent and there was slight postmortem diffusion over the back. The conjunctivae were clear and glistening. The pupils were widely dilated, equal and regular in outline. A few light colored hairs were present on the head. The fontanels were open, depressed and of normal size. There was no evidence of bony abnormalities of the head or hydrocephalus. The superficial lymph nodes were not palpable. The chest was symmetrical. There was a

Figure 4

postoperative wound, 3½ inches long, over the right rectus muscle, extending from 1 inch below the costal margin to just below the umbilicus. There was another wound, 1 inch long, with a No. 16 catheter leading from it situated over the left rectus muscle, 1 inch to the left of the midline, and 1½ inches below the costal margin. Both of these operative wounds were fresh and had been sutured with silkworm gut and plain catgut.

On opening the abdomen, the cavity was found to contain large quantities of clotted blood. Some fluid was also present. Near the operative wounds were fibrinous adhesions between the bowels, stomach and anterior abdominal wall. The catheter was found to lead into the stomach, which was sutured to the abdominal wall around the smaller wound. The point of origin of the hemorrhage could not be located, the blood probably escaping, however, from the incision in the stomach.

On opening the chest, the thymus was seen as a mass of pinkish tissue in the upper mediastinum, appearing normal to the naked eye. The pleural

cavities were dry and free from adhesions. The lungs, except for areas of atelectasis at the bases, were natural. The pericardium was smooth and glistening. The heart was normal in size and the endocardium throughout appeared normal. The ductus venosus, ductus arteriosus and foramen ovale were closed, and the normal circulation appeared to have been established. The aorta and pulmonary arteries were smooth and elastic.

The whole intestinal tract, from the cardiac end of the stomach to the anus, was traced and found to be patent. It contained soft, dark meconium. The esophagus was patent as far as the level of the fourth dorsal vertebra, where it ended blindly in a dilated pouch. This pouch was situated just at the bifurcation of the trachea, and just above the arch of the aorta. From this point on, the esophagus was represented as a fibrous band, to within about 1 inch of the stomach, where it again became a patent tube to empty into the stomach. A probe passed up from the stomach showed that this portion ended in a blind pouch about 1 inch from the stomach. No fistula was present between the esophagus and stomach in any part of its course. Microscopic examination of the esophagus showed nothing remarkable.

The other organs revealed nothing worthy of record in the present connection.

CASE 2.—*History.*—A baby girl was born of healthy parents on the obstetric service of Bellevue Hospital. The child at birth presented a malformation of the right forearm which was found to be due to failure of development of the lower two-thirds of the radius. It was noticed a few hours after birth that water given by mouth was vomited at once. The swallowing of fluid was associated with definite asphyxial attacks, lasting about one minute. On attempting to feed the child by gavage, it was found that a soft rubber catheter could not be passed farther than a point 4 inches from the child's lips. The catheter was passed under the fluoroscope ·and was seen to be prevented in further passage at the level of the third rib posteriorly. A diagnosis of congenital atresia of the esophagus was made.

Examination.—The physical examination was negative, except for the above findings, and the presence of a moderately distended abdomen.

The roentgen-ray findings were obtained by giving the child about 2 c.c. of esophagus contrast salt mixture. The radiographer reported a congenital obliteration of the esophagus below a point opposite the second dorsal vertebra. At this point there appears to be a connection between the esophagus and trachea. A considerable amount of contrast salt was introduced into the lungs, outlining the bronchial trees on both sides.

Surgical Treatment.—It was decided that gastrostomy offered the only hope of dealing with the condition. This was done by Dr. C. G. Burdick under light ether anesthesia. High right rectus incision revealed at once a much dilated stomach. In the anterior wall a soft rubber catheter was inserted through a small puncture and maintained in position by inverting the stomach with three circular purse-string sutures. The site of the gastrostomy was anchored to the original abdominal wound, which was then closed above the catheter in the usual way. Following operation the child was given small amounts of sterile water and later breast milk by way of the catheter. It was later noticed that the child brought up from the throat a small amount of brown stained material mixed with mucus. The child lived twenty-eight hours after the operation. No necropsy was performed, permission having been refused by the parents.[16]

16. The following references may also be consulted:

Dam: Cas d'imperforation de l'oesophage, Policlin., Brux. **15**:196, 1906.

Patron, P.: Malformation congenitale de l'oesophage; imperforation oesophagienne et communication oesophago-tracheale, Gaz. méd. de Nantes **24**:573, 1906.

Dickie, D.: A Case of Congenital Malformation of the Esophagus, Brit. J. Child. Dis. **3**:451, 1906.

Vielliard and LeMee: Obliteration congenitale de l'oesophage, Bull. Soc. de pediat. de Par. **8**:411, 1906.

Spicer, J. E.: A Case of Abnormal Development of the Esophagus, Lancet **1**:157, 1907.

Wunsch, M.: Ueber einen angeborenen Bildungsfehler der Speiserohre (wahrscheinlich angeborener Verschluss derselben), Med. Klin. **3**:389, 1907.

Guyot, J.: Malformation de l'oesophage thoracique avec occlusion du bout superieur et abouchement du bout inferieur dans la trachea, Bull. et mem. Soc. anat. de Par. **82**:327, 1907.

Griffith, J. P. C., and Lavenson, R. L.: Congenital Obliteration of the Esophagus, with Report of a Case, Am. J. Obst. **58**:554, 1908.

Phillips, J.: Congenital Malformation of the Esophagus, with Report of a Case, Arch. Pediat. **25**:267, 1908.

Giffhorn, H.: Beitrag zur Aetiologie der kongenitalen Atresia des Oesophagus mit Oesophagotrachealfistel, Virchows Arch. f. path. Anat. **192**:112, 1908.

Cameron, J. A., and Lightaller, G. S.: A Case of Congenital Malformation of the Esophagus, Australasian M. Gaz. **28**:137, 1909.

Gilbert, P., and LeMee, J.: Note sur un nouveau cas d'imperforation congenitale de l'oesophage, Bull. et mem. Soc. anat. de Par. **84**:94, 1909.

Lateiner, M.: Ein Fall von angeborener Oesophagus-Atresia mit Trachealkommunikation, Wien. klin. Wchnschr. **22**:53, 1909.

Von der Porten, E.: Ein Fall von Atresia oesophagi congenita mit Oesophagus-Trachealfistel, Deutsch. Ztschr. f. Chir. **98**:578, 1909.

Clark, J. P.: Congenital Web of the Esophagus, Report of a Case, Laryngoscope **21**:810, 1911.

Fabre and Trillat: Imperforation de l'oesophage, Bull. Soc. d'obst. et de Gyn. de Par. **1**:42, 1912.

Konopacki, M.: Ueber einen Fall von Angeborenen partiellan speiserohrendefekt (atresia oesophagii) als Beitrag zur Entwicklung der Luftrohre beim Menschen, Centralbl. f. allg. Path. u. path. Anat. **23**:386, 1912.

Pollack, R.: Atresie des Oesophagus und Kommunikation zwischen Magen und Trachea, Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **11**:200, 1912.

Anderodias, J.: Malformations des voies aeriennes et digestives superieures chez un enfant nauvean-ne; imperforation de l'oesophage et communication oesophago-tracheale, J. de méd. de Bordeaux **43**:646, 1913.

Flesch, H.: Diverticulum oberhalb einer narbigen Oesophagusstenose, Jahrb. f. Kinderh. **78**:83, 1913.

Jackson, J. B.: A Case of Congenital Atresia of the Esophagus, J. Mich. M. S. **14**:193, 1915.

Berblinger: Partielle Atresie des Oesophagus, Kommunikation zwischen Trachea und unterer Speiserohrenhalfte, München. med. Wchnschr. **115**:113, 1918.

St. George, A. V.: Congenital Atresias and Stenoses of the Gastro-Intestinal Tract, Proc. New York Path. Soc. **18**:32, 1918.

THE USE OF SUPPORTS IN OBSCURE ABDOMINAL CONDITIONS *

LLOYD T. BROWN, M.D., AND FRITZ B. TALBOT, M.D.

BOSTON

This article supplements our previous paper on bodily mechanics in its relation to cyclic vomiting and other obscure abdominal conditions.[1]

In the first communication it was thought wise not to emphasize the abdominal support but to show the connection between poor bodily mechanics, constipation, cyclic vomiting and acute abdominal pain. Emphasis was laid in that paper on the necessity of a complete medical examination, an examination of the stools and regulation of diet. Especial attention was called to the necessity of rest periods which are ordered for all these patients to prevent and relieve the great fatigue under which they are living. The use of body supports was mentioned but not described in detail because it was felt that undue emphasis would be laid upon the part that the abdominal support plays in the cure of these conditions.

There is unquestionably much danger associated with the indiscriminate use of abdominal supports for children as well as for adults. This paper is written for the purpose of showing the mechanical conditions in which the need of supports is indicated, why they should be used, and the correct method of fitting them to the patient.

The chief purpose of the abdominal support is to relieve the general body fatigue which is always present when the body mechanics are incorrect. When the posture is improper and the child is fatigued, there is always a relaxation of many of the muscles of the body. This is often most evident in the abdominal muscles. When these muscles become relaxed, the abdomen protrudes forward and sags. In this type of child the lower abdomen, that is, the part below the umbilicus, appears larger and has a greater circumference than that above the umbilicus (Fig. 1). The illustrations in the first publication also show this very well.

The following description will be clearer if each factor is studied in Figure 1. Associated with the relaxed, protuberant abdomen there is always an increase in the lumbar curve of the back (lordosis). This lordosis necessitates, by the laws of mechanics alone, even if there were no other elements present, a compensatory forward curve in the

1. Talbot and Brown: Am. J. Dis. Child. **20**:168 (Aug.) 1920.

dorsal spine with a backward displacement of the thorax in relation to the abdomen and hips. This increased forward dorsal curve and backward displacement of the thorax is compensated for by a forward position of the head. The forward position of the head relaxes the accessory muscles of respiration, the sternocleidomastoids, etc., as well as the suspensory ligament of the diaphragm, and allows the chest and sternum to settle downward. This, in turn, relaxes the abdominal muscles, and thus makes possible the relaxed prominent abdomen always present in these cases.

Fig. 1.—This child was referred to the clinic because of very obstinate constipation. Note the characteristic appearance and the very bad bodily mechanics (See text).

This very brief description brings out the fundamental principle that is the basis of all mechanical treatment, namely, that a change in one part of the body is always accompanied by a greater or lesser change in every other part of the body. Just where this change will occur varies, of course, in each individual according to the anatomic type.

In a case of poor bodily mechanics, in which it is necessary to fit a support, one must first consider what part of the body is most relaxed and needs support, and how much of a support is necessary to accomplish the desired results. In order to recognize the abnormal bodily mechanics, it is necessary to have a thorough knowledge of the normal bodily mechanics. This knowledge comes only with experience and careful study of the mechanical principles involved.
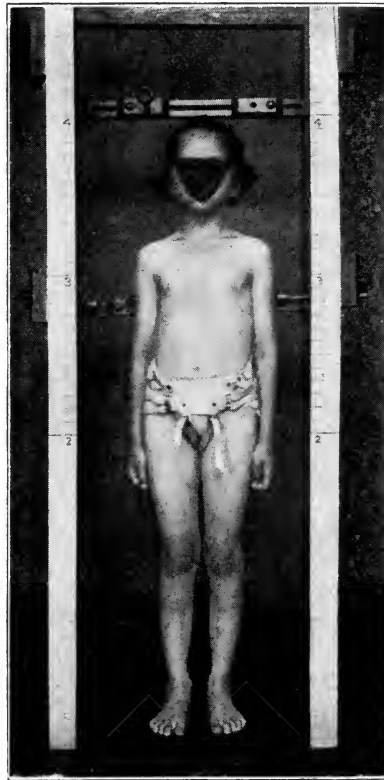
Fig. 2.—Shows child with anterior pad in position.

There are many degrees of abnormality, and it is, therefore, impossible to give any definite rules in regard to the amount of support necessary in cases of poor bodily mechanics as it varies in each individual case, but in general, the greater the fatigue the greater the indication for support, and the larger the support will have to be. The general appearance of a patient will sometimes give an idea of the amount of fatigue present, but in order to form a good opinion, one should always take into account the general factors of habits and hygiene before deciding on the amount of fatigue.

Some postures are so poor that a permanent deformity is associated with the bad mechanics. By permanent deformities we mean such conditions as the curvatures found in structural lateral curvature, forward curved dorsal spine, which is very stiff to extension, or shoulders which droop forward, associated with pectoral muscles contracted because of long standing faulty position of the body. Deformities may occur in any part of the body where the muscles become contracted by long use of an improper position.

Fig. 3.—Shows child with posterior pad in position.

Two general types of supports may be used: (1) the smaller or so-called anteroposterior pad, which gives support to the abdomen and lower back alone, and (2) the spring back brace, which supports the abdomen, back and shoulders.·

The former is usually indicated in mild cases of poor mechanics, or during convalescence from the more severe grades in which a back brace had been used for a time. This anteroposterior pad consists

of two leather pads, one for the front and the other for the back, and is made of two pieces of leather lined with felt. The leather, which is next to the skin, is soft, while the outer piece is somewhat stiffer. The pads are built up on a framework of light steel to which the outside leather and buckles for the straps may be attached. The front pad is made in the shape of a parallelogram with the two lower corners cut off so that it will fit below the umbilicus and over the

Fig. 4.—Shows how the anteroposterior pad tends to improve the mechanics of the abdomen. The improvement of the bodily mechanics as a whole can only be accomplished by postural education. Compare with Figure 1.

muscles of the lower abdominal wall (Fig. 2). The back pad (Fig. 3) is also the shape of a parallelogram, except that the upper end is wider than the lower end. The pad should be made long enough to extend from the cleft of the buttocks to the eleventh or twelfth rib. This is of great importance. If it is made too short, the upper body will be able to lean backward over the top of the pad, thus causing an

increase of the lumbar curve, and although apparently effecting what is desired for the abdomen, it would intensify the original anteroposterior curve and do harm to the patient.

The pads of this anteroposterior belt are connected by three straps. The top strap should come just above the iliac crests (Fig. 4), and the bottom strap placed at the sides, so that it will come just between the trochanter and the crest of the ilium. The perineal straps are fastened to the bottom strap, at a point just back of the trochanters
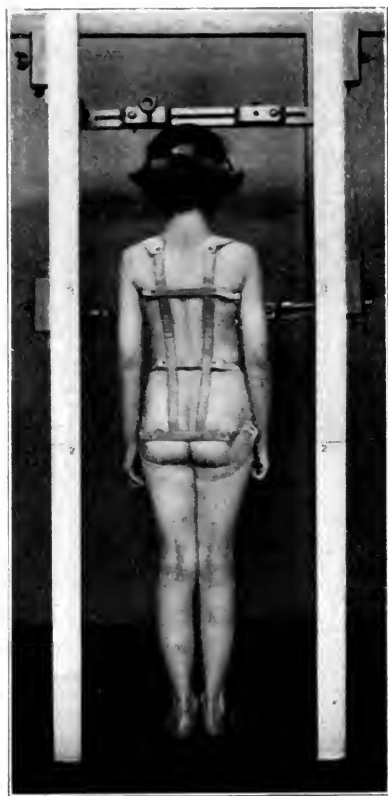
Fig. 5.—Shows the spring back brace on the child (rear view).

for the purpose of keeping it from slipping up on the abdomen. This anteroposterior belt should be worn snugly. Educational exercises should be given at the same time.

The other support, that is, the spring back brace, is made of a tempered spring steel about 18 to 20 gage and is covered with felt and leather. The measurements for the steel are taken from the lower end of the sacrum to about one inch above the spine of the scapula (Fig. 5). There are two uprights, from one and a half to two inches

apart at the bottom, and from three to four inches apart at the top, or enough to make the uprights come over the scapulae and not directly over the erector spinae muscles. There are three crossbars, one at the bottom, to which is fastened the lower strap of the front pad, worn in connection with the brace; a second one at a point just above the crests of the ilia, to which is fastened the top strap of the front pad, and one at the top placed at the level of the axilla behind or about one inch above the lower border of the lower angle of the
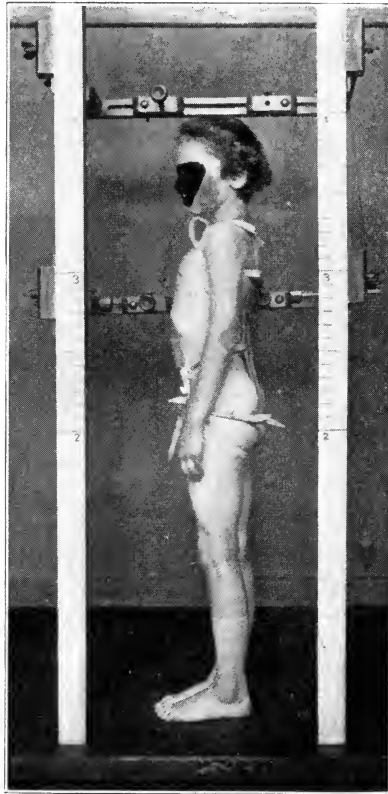
Fig. 6.—Shows child with spring back brace on. Compare with Figure 1 and note the change in the bodily mechanics.

scapula. This position is important because if it is too low the scapula will have a tendency to ride up on the crossbar and be very uncomfortable.

This brace is usually made up in the rough at the shop and sent to the orthopedic surgeon to be fitted to the child before the steel is tempered. The fitting is a matter of considerable importance and should never be left to the instrument maker. The main point to be

remembered in the fitting of the brace is that it is applied to prevent the child from assuming the habitual extremes of the faulty mechanical positions, and it should, therefore, be fitted to the child with the body in the best position that can be assumed. Since the brace is made of spring steel it consequently allows a considerable amount of motion, at the same time preventing the extreme faulty position (Fig. 6).

We wish to emphasize again that neither of the braces described will permanently prevent the child from assuming the faulty postures

Fig. 7.—Note the extreme faulty posture, especially the flat chest and the abdomen that is more protuberant below the umbilicus than above. This child is Case 2 of our previous communication. Compare with Figure 8.

and they are not put on with that idea in view, but merely to rest the child by lessening the amount of muscle strain, and to help correct the faulty habits of posture.

The wearing of the braces should always be accompanied by educational exercises, except in the case of very young children. These exercises are planned primarily to teach the child how to use its body

in good mechanics and secondarily to strengthen or increase the size of the muscles.   Since the child is fatigued to a greater or less degree as a result of the poor body mechanics, rest is much more important than exercise, and for the first week, at least, the child is asked to lie down with a pillow under its lumbar and lower dorsal spine so that the ribs are expanded while the head and buttocks rest on the table. Breathing exercises can be performed in this position and help stretch the contracted chest.
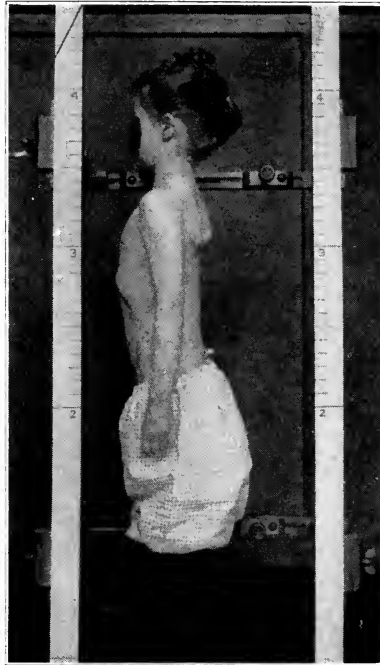
Fig. 8.—Shows the same child as shown in Figure 7 after postural training. Note the change in the shape of the abdomen caused by contraction of the abdominal muscles. Also the flattening of the lumbar curve which is accomplished by gluteal contraction. Note also the position of the head.

The next step is to teach the child the correct standing position. In this procedure, two separate groups of muscles are used which must come into play before it can be accomplished successfully. First, the child must learn how to contract the gluteal muscles. This will flatten the lumbar spine. Second, the muscles of the lower abdomen, below the umbilicus, should be contracted, thus pulling in the lower abdomen and forcing the intestines upward into their normal position. This will relieve the strain on the mesentery. Finally, holding this position, the head should be held up straight with the chin in. This will draw up the chest to its proper position. After the child has learned how to

control the muscles involved in these movements and can assume a correct standing position, other exercises may be given. The exercises should always be done with the body in good posture. If the correct posture cannot be maintained, the exercises should not be considered beneficial since the prime object of all the exercises is simply to educate the child to use its body in good mechanics. Figures 7 and 8 show the results which may be obtained by postural training supplemented by temporary use of the brace.

CONCLUSION

In conclusion we wish to emphasize again the fact that mechanical supports are only temporary makeshifts, the purpose of which is to break up the bad habits of posture and relieve the fatigue. They should, of course, be dispensed with at the earliest possible moment. Education of the muscles is in reality the most important element in the treatment, but it often has to be accomplished with the aid of mechanical supports until the muscles are strong enough to take up the burden themselves. When possible, treatment should be carried out without the use of supports.

KERATOSIS DIFFUSA FETALIS (ICHTHYOSIS CONGENITA)*

JULIUS H. HESS, M.D., AND OSCAR T. SCHULTZ, M.D.

CHICAGO

NOMENCLATURE

The term "ichthyosis," derived from the Greek word $ἰχθύς$ (fish), has been used to designate keratosis, a condition in which the skin bears a fancied resemblance to the skin of fishes. It is, however, only in rare cases that the skin resembles somewhat the fish skin, the comparison appearing to be far fetched in the majority of cases of keratosis, both in the mild and in the severe variety. In the latter, the skin has more properly been likened to tortoise shell; skin of a baked apple; skin of potatoes cooked in water; dry yellow leather (morocco leather); armor of crustaceans, bark of trees, skin of a serpent, crocodile skin, etc. A number of names for these conditions have been derived from the gross appearance of the skin such as ichthyosis, fish skin disease, xeroderma (dry skin), xeroderma ichthyoides, sauriasis, crocodile skin, alligator skin, harlequin fetus. Riecke[1] made the most thorough recent study of the condition and gives the literature to 1900. Ballantyne's[2] book gives the older bibliography.

All these terms are based on a predominating and most striking symptom of the condition. It is, therefore, the variation in the intensity of the symptom which varies the name of the disease from ichthyosis to sauriasis or xeroderma. This nomenclature leads to a great variety of terms, each of which emphasizes a special predominating symptom or gross pathologic condition of the skin and conveys the idea that this predominating symptom is the essential component of the condition. It ignores the pathologic anatomy which is common to all these conditions, at least qualitatively, and which is the essential change, the variations in the clinical picture depending on the severity of the pathologic changes.

A number of names derived from the pathology of the condition have been proposed to designate what has been called "ichthyosis."

1. Riecke: Ueber Ichthyosis congenita, Arch. f. Dermat. u. Syph. **54:**289, 1900.

2. Ballantyne: The Diseases and Deformities of the Fetus. Edinburgh, Oliver & Boyd, 1892-1895.

Among these are keratosis diffusa epidermia intrauterina (Lebert), because the main seat of the histologic processes is in the epidermis and the most striking is the enormous hyperplasia of the stratum corneum; universal diffuse keratoma (Kyber); hyperkeratosis diffusa congenita (Eppinger). .

Keratosis may be defined as an abnormal cornification of the skin and, theoretically at least, keratoses may be classified as hypokeratosis and hyperkeratosis (quantitative abnormalities), and parakeratosis or dyskeratosis (qualitative abnormalities), and a combination of quantitative and qualitative abnormalities. Most of the affections classified under the keratoses consist of increased and abnormally altered cornification. The term keratosis is more appropriate than hyperkeratosis to designate the affection that has been named "ichthyosis," since this condition is a combination of hyperkeratosis and parakeratosis.

The two affections which have been called ichthyosis simplex (or vulgaris) and ichthyosis congenita are generally admitted to be congenital affections, some regarding them as congenital anomalies of the development of the skin. The term "congenita" therefore, is not only superfluous, but it leads also to confusion, conveying the idea that one form is congenital and the other form (simplex, vulgaris) not congenital, which, however, is not the case. Since, further, the affection which we are about to describe, develops during fetal life and is almost always diffuse, in contradistinction to the simplex form, which as a rule develops during the first year of life and usually is not universal, we believe that this keratosis should be designated "keratosis diffusa fetalis," under which term we are going to describe the affection.

DEFINITION

Keratosis diffusa fetalis may be defined as an independent congenital developmental anomaly of the skin, of unknown etiology, characterized by diffuse, usually general hyperkeratosis and qualitatively abnormal cornification of the skin with decreased exfoliation of the epidermis. This combination of processes causes the formation of thick horny scales with intervening deep fissures, the skin resembling a horny cuirass. Secondarily, it results in arrest of development and in deformities of the external ears, eyes, nose and lips, the latter symptoms usually being already present at birth; occasionally, however, they may be very slight or entirely absent at this time. The condition usually terminates fatally even in the absence of any assignable cause.

SYMPTOMS AND CLINICAL TYPES

The most characteristic in the clinical picture of this condition are the skin changes and the secondary malformations of ears, eyelids,

nose and lips. The course of the disease depends primarily on the intensity of the skin changes. Basing his classification on the intensity of the skin changes, especially as seen at birth, Riecke divides the cases of keratosis diffusa fetalis into three types.

Keratosis diffusa fetalis (ichthyosis congenita par exochen, Riecke) comprises the cases with high grade anomalies of the skin and with resulting disturbances of growth. In these cases the condition is
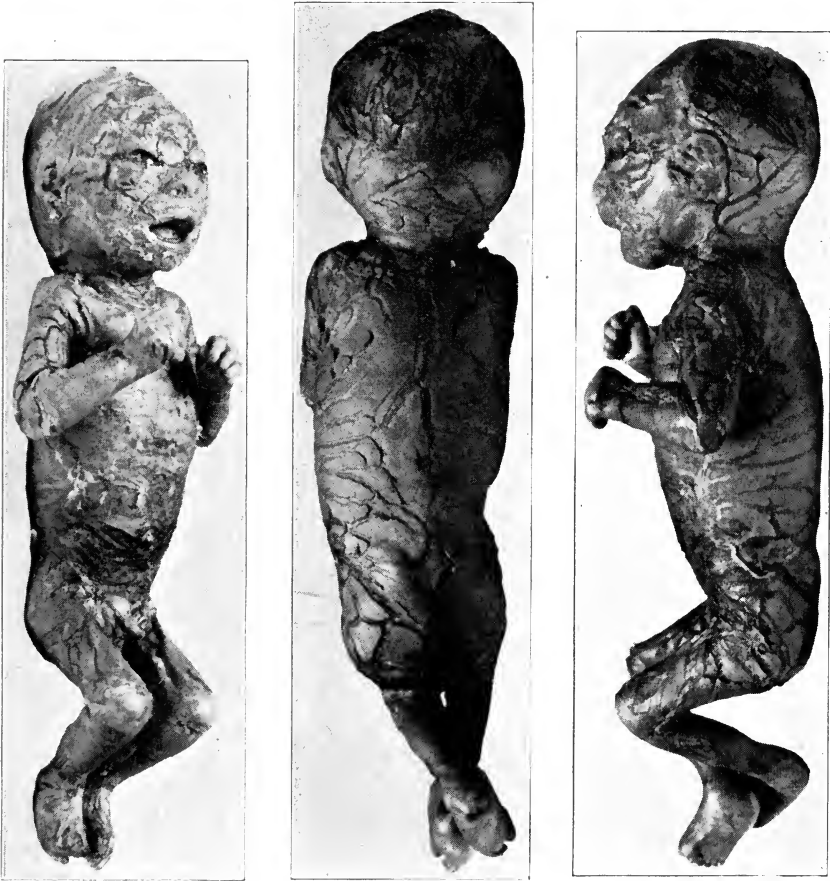
Figs. 1, 2 and 3.—View of whole infant, illustrating the external characteristics.

already fully developed at birth, presenting a fairly constant and uniform clinical picture and these children are not viable. The longest period of life which was observed was 9 days (Jahn[3]). On the average, the infants died after three days, and only rarely were they

3. Jahn: Ueber Ichthyosis congenita. Inaug. Diss., Leipzig, 1869.

born at full term. The fetuses or infants belonging to this group may be described about as follows: The entire surface of the skin is formed by thick, tough, horny shields and plates, mostly of yellowish gray color, and about 0.5 cm. in thickness. They are of manifold configuration, round, oval, triangular, quadrangular, rectangular and of different sizes. Between the plates there are numerous fissures

Fig. 4.—Face, neck and hands of patient.

varying in width and depth, sloping down either abruptly and almost perpendicularly from the plate, or a gradual, slow transition takes place. Some fissures are provided with a thin epithelial covering; frequently, however, the corium is freely exposed. Hands and feet take no part in the formation of plates and fissures. In most cases the hands and feet are clubbed and they are covered by smooth, shiny,

tough, thickened skin. The genitals are normally developed in some cases, in others they are rudimentary. Ectropion of their skin folds is the rule.

Just as typical as the abnormal condition of the skin are the anomalies in the form of the face that are found in the individuals belonging to this group. Lanugo hair covering is frequently absent, and cilia and supercilia frequently do not develop. The eyelids are rudimentary in the shape of horny plates, and in the position of extreme ectropion, so that the conjunctiva is prominent in the shape of red, raw tumors below which the otherwise normal eyebulb is hidden. The

Fig. 5.—Hands of patient.

nose is flattened, frequently barely rising above the level of the surrounding skin of the face. The nasal openings are narrowed and occasionally only one is found patent. Both lips are highly ectropied, so that both alveolar processes are well seen. The mouth is continuously open, resembling thus the mouth of fishes. The lobules of the ears are never distinctly developed. Occasionally the formation of the ear is indicated only in the skin of the ear, the lobules of the ear being as in bas relief. The presence of the auditory canal may in most cases be demonstrated by sounding only, since it is a very narrow fissure.

The infants born with severe keratotic changes of the skin, as described above, persistently hold their extremities in the fetal attitude. There is very little movement and the breathing is shallow, almost imperceptible. The mouth cannot be closed, nor opened any wider, and this condition markedly interferes with proper nursing. The stiffened condition of the skin is undoubtedly responsible for the diminished mobility of the infant.

Almost one-half of all cases of keratosis diffusa fetalis belong to this group.

Keratosis diffusa fetalis mitior (ichthyosis congenita larvata, Riecke) comprises those cases in which the condition is not fully developed at birth, the degree of development especially of the skin changes varying in different cases. While all the children of the first group die in a few days, those of the second group may survive for a

Fig. 6.—Soles of feet.

much longer time. About one-half of these children were born premature, the other half being full-term infants. While the clinical picture presented by the cases of the first group is fairly uniform in symptoms and clinical course, there are considerable differences in the intensity of the changes in different cases and, therefore, also in the course of the disease in the second group. The intensity of the process often varies in different regions of the body.

In some cases, while there are marked anomalies in the formation of the face, the skin may be of more or less normal appearance. In other cases, plate formation and fissuring of the integument is the most striking symptom, while the face shows only very little abnormality. Or, on the other hand, the slightly scaling skin presents numerous folds all over the body, so that it appears to be loose and

too wide; on the extremities, however, it may be tightly adherent to the subcutaneous tissue, thin, shiny and desquamating in large flakes. Frequently the skin all over the body is thin, atrophic, parchment-like, dry, shiny and traversed by fissures and furrows, and covered with scales of tissue paper character. To this latter condition refers the comparison to thin collodium film made by many authors or to a coat of varnish or to cracked porcelain glaze.

There may also be considerable variation in the intensity of the anomalies in the development of the face. Extreme ectropion of the upper lip may be present while the lower lip may be more or less
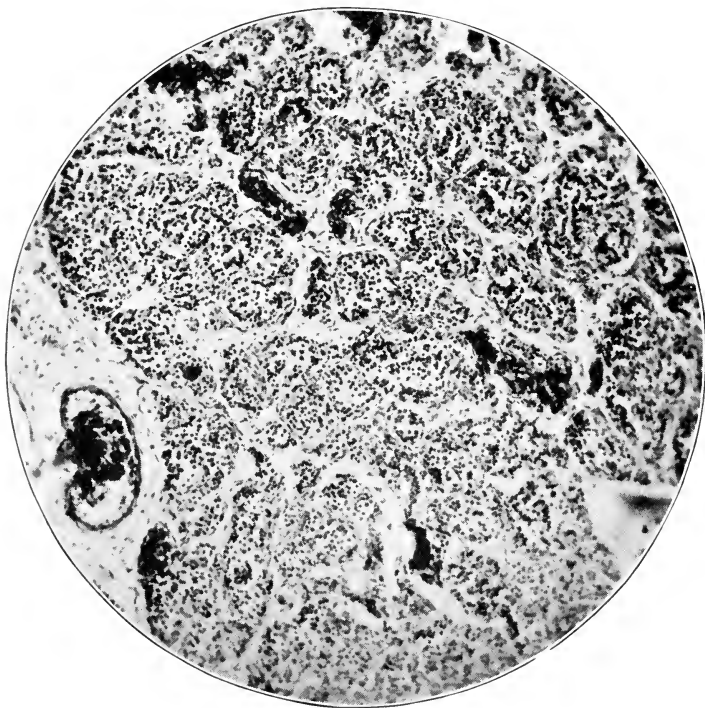
Fig. 7.—Thyroid. The tissue is undifferentiated. Photomicrograph, $\times$ 110.

normal. A high grade ectropion of the eyelids may be present, while the nose and the ears may be normal in their appearance. Or with a well formed nose, the lips may be markedly everted and every trace of the ear lobules absent; or with a normal development of the latter, the deformity of the nose may be the most striking symptom.

The third group, *keratosis diffusa fetalis tarda,* (ichthyosis congenita tarda, Riecke) is marked less by its clinical peculiarities than by its peculiar clinical course. In the cases belonging to this group,

the above described anomalies are only slightly developed at birth, or the infants may be born without any visible changes on the part of the skin or of the face. The viability of these infants, provided they are not born prematurely, is scarcely influenced by the condition. Only after days, weeks or months the symptoms develop which finally lead to the picture of milder keratosis diffusa fetalis. It is remarkable in these cases that with the development of the external anomalies the general development of the entire organism almost always suffers. The further existence of these cases depends on the final degree of development of the keratosis provided no intercurrent condition causes death, and the individuals may remain alive for months or even years.
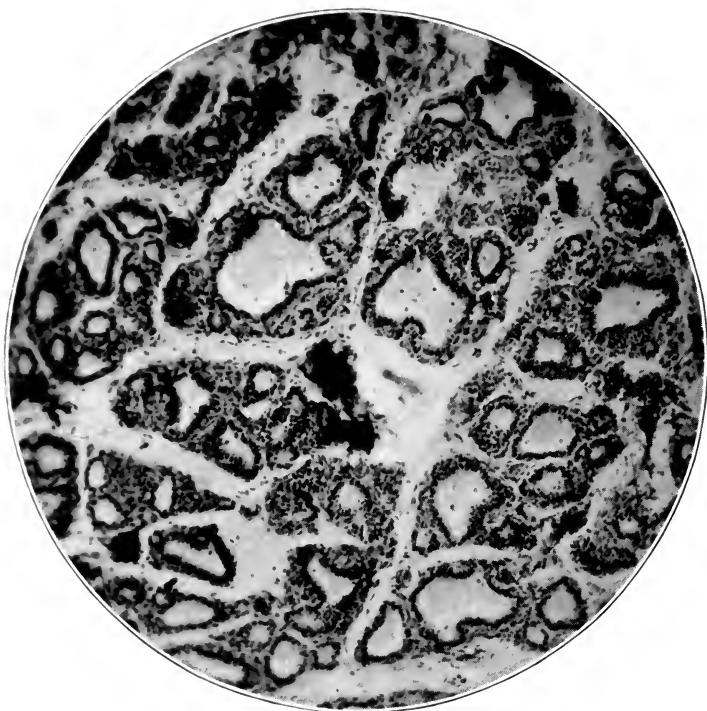
Fig. 8.—Thyroid. Differentiated, functioning follicles in one of the four small areas of such tissue present. Photomicrograph, × 110.

There is a striking similarity, not only in the condition of the external integument and of the formation of the face, but also in the clinical picture, in that the anamnesic data are almost the same. The abnormal condition of the skin was noticed immediately after birth or, on the other hand, after a longer period, mostly of several years duration.

Two cases reported by Munnich [4] belong to this group. Two children of the same family were affected, and it is interesting that the appearance of the affection was preceded by redness of the skin, which has also been observed by Haus [5] in paratypical ichthyosis and many horny nevi. At the time of birth, the condition was only very slightly developed and longer life was possible.

Fig. 9.—Skin of the back. A central group of three elongated papillae is covered above by the greatly thickened horny layer, only the lowermost layer of which is shown, and is separated on each side from the neighboring groups of papillae by large, whorllike masses of keratinized epithelium. Photomicrograph, × 110.

Lang [6] reported the cases of two children in the same family. The older child was prematurely born, and the first symptoms of the disease appeared in the third week, while in the other child, born at full-term, the affection began in the second month of life. In these two children, features characteristic of keratosis diffusa fetalis were

4. Munnich: Monatsch. f. prak. Dermat. **5**:240, 1886. (See Riecke, Ref. 1.)

5. Haus: Ichthyosis congenita (hyperkeratosis diffusa congenita). Norsk. Mag. f. Laegvidensk. **16**:542, 1901.

6. Lang: Tageblatt d. 58 Versamml. deut. Naturfursch. u. Aertzte in Strassburg, 1885, p. 295 (See Riecke, Ref. 1).

later seen, namely ectropion, involvement of the eyes, deformities of the ears, and of the anus, absence of panniculus, parchment-like skin, flexion contractures, shortening of the fingers with deformity of the nails, and disturbances of the general growth. Abscesses appeared, and death occurred at the age of 27 and 15 months, respectively.

Róna's [7] cases are of special interest because of the fact that the author was able to observe personally the development of the process and did not have to rely merely on anamnesic data that are not always reliable.
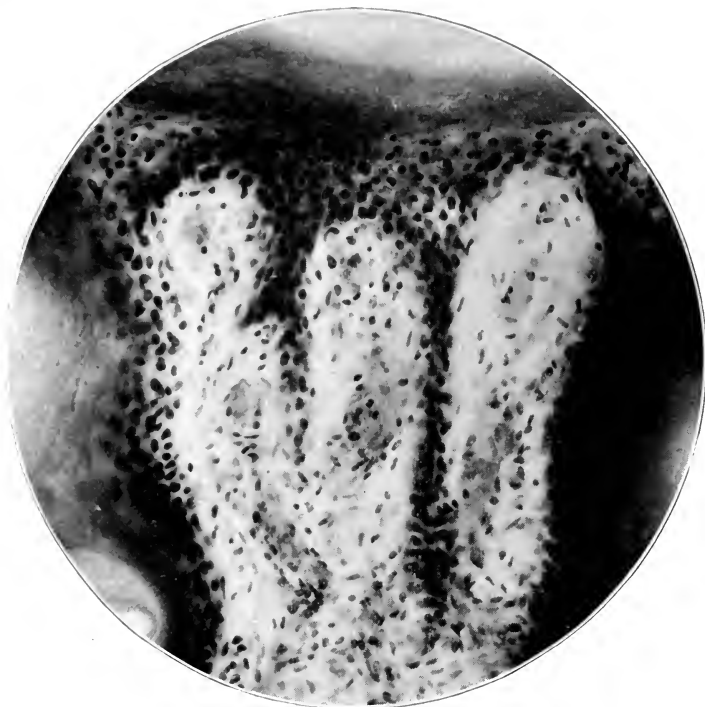
Fig. 10.—Skin of the back. The epidermal covering of the elongated papillae. The transition from nucleated to nonnucleated epidermis is very abrupt. The deeper half of the nonnucleated portion contains fine hematoxylin staining granules. Photomicrograph, × 230.

The cases of the third group show in their course a certain relationship to other forms of keratosis, e. g., keratosis palmaris and plantaris (Bruhns,[8] Dore [9]), which become noticeable in the first weeks

7. Róna: Hochgradige Ichthyosis im Säuglingsalter, Arch. f. Dermat. u. Syph. 21:339, 1889.

8. Bruhns: Die atypischen Ichthyosfälle und ihre Stellung zur Ichthyosis congenita und Ichthyosis vulgaris. Arch. f. Dermat. u. Syph., 113:187, 1912.

9. Dore: A Case of Congenital Hyperkeratosis of Palms and Soles, Proc. Roy. Soc. Med., London 7:35, 1913.

of life, but reach the highest degree of their development only after several months. In this respect they remind one of certain keratoid nevi, of which usually nothing is seen at birth. Some, at least, of the cases of ichthyosiform erythroderma, which have been collected and analyzed by MacKee and Rosen,[10] appear to belong to this group.

PATHOLOGY

Marked pathologic changes are almost entirely limited to the epidermis, the most characteristic being hyperkeratosis, the cutis showing only slight inflammatory changes (Wassmuth[11]), which may well be

Fig. 11.—Skin of the back. The skin at the bottom of one of the fissures. The entire thickness of the horny layer is shown. The cellular epidermis is thin and the papillae are short, widely separated and oblique. The deeper tissue is edematous. Photomicrograph, $\times$ 125.

due to secondary infection. In a few cases pathologic changes have also been found in glands of internal secretion (thyroid, thymus, suprarenals). Interesting is also the intense congestion of many organs of

10. MacKee and Rosen: Erythrodermie congénitale ichthyosiforme. Report of Cases with a Discussion of the Clinical and Histologic Features and a Review of the Literature, J. Cutan. Dis. **35**:235, 343, 511, 1917.

11. Wassmuth: Beitrag zur Lehre der "Hyperkeratosis diffusa congenita," Beitr. z. path. Anat. u. z. allg. Path. **26**:19, 1899.

the body (kidney, liver, meninges of the brain, etc.) similar to that occurring after severe burns where a large portion of the skin is destroyed. In most cases no particular pathologic change or group of changes was found that could be designated as a direct or ultimate cause of death.

Epidermis, dermis and subcutaneous tissue were found to be present in all cases, the subcutaneous tissue and the dermis being either normal or showing slight secondary changes. The different layers of the epidermis are more or less preserved, and Wassmuth differentiated even five layers of the epidermis. His observation, however, has not been confirmed by other investigators.
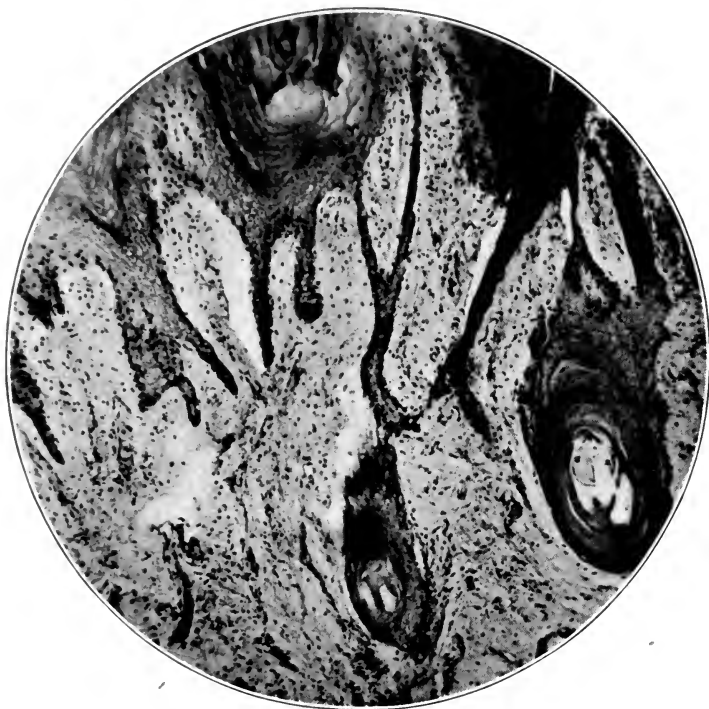
Fig. 12.—Skin of the scalp. The papillae are very long, branched and edematous. The cellular epidermal layer is very thin. Two hair follicles are shown, one of which is almost completely cornified. The greatly thickened stratum corneum is not shown. Photomicrograph, ✕ 90.

Enormous thickening of the stratum corneum is the most striking and the most constant pathologic change. Its thickness varies in different regions of the body, being thinnest on the abdomen (0.2 mm.) and thickest on the scalp (up to 5 mm.), averaging about two hundred times thicker than normal (Wassmuth).

According to some authors (Schabel,[12] von Schab [13]) the stratum corneum is homogenous, bearing, however, a distinct indication of its elementary structure. Claus [14] has observed nuclei and nuclear remnants in this stratum. Wassmuth found it to be very irregular in structure, composed of lamellae superimposed in wavelike manner and in general parallel to the surface, and of layers with keratohyalin and keratin granules. Other authors (Koller,[15] Stühlinger [16]) were able to demonstrate cellular structure only in the lowermost layers of the stratum corneum. Jahn [3] has isolated flat epidermal cells from this layer. Riecke thinks that it is a mistake to regard the horny deposits as homogenous, but he remarks that he found the stratum corneum to be completely developed, although the fetus was premature. Unna [17] says that the horny cells are homogenous and contain no nuclear remnants which are normally present.

Meyenburg [18] states that qualitatively the horny layer seems to be similar to that found on the palm of the hands and the soles of the feet, therefore of normal chemical composition and only excessive in amount, i. e., simple hyperkeratosis. Wassmuth, on the basis of differential staining methods and of digestive experiments, comes to the conclusion that the epidermic horny plates are not formed of normal corneal substance, but rather by cells in the stage which immediately precedes cornification. Von Bärensprung [19] found that these plates contain large quantities of ash and especially of iron and silicates. Riecke states that although there are some deviations from the normal in the nature of staining of the stratum corneum, this method does not furnish a sufficiently safe basis for estimation of cornification of this layer, nor for the formulation of a hypothesis as to the development of this anomaly, and that the elements composing the horny deposits proved to be, wherever they could be recognized, always ordinary horny cells and by experiments with digestive tests their nature in all horny plates may be proven.

12. Schabel: Ichthyosis congenita. Inaug. Diss., Tübingen, 1856.

13. Von Schab: Drei Fälle von congenitaler Ichthyose. Inaug. Diss., München, 1889.

14. Claus: Ichthyosis congenita. Inaug. Diss., Berlin, 1897.

15. Koller: Ein Fall von Ichthyosis congenita. Inaug. Diss., Leipzig, 1894. (Unpublished thesis; see Riecke).

16. Stühlinger: Ein Fall von Ichthyosis congenita. Inaug. Diss., Marburg, 1880.

17. Unna: The Histopathology of the Diseases of the Skin. Translated by Norman Walker. Edinburgh, W. F. Clay, 1896.

18. Meyenburg: Ein Fall von Ichthyosis congenita. Inaug. Diss., Berlin, 1912.

19. Von Bärensprung: Die Hautkrankheiten. Erlangen, F. Enke, 1859.

Meyenburg found cell remnants and enclosed masses of detritus in the stratum corneum, but he has observed neither enclosure nor displacement of epithelium. Almost all other authors, however, who have studied the histopathology of this condition have found structural abnormalities and peculiar and interesting formations, consisting of concentrically arranged lamellae of horny cells enclosing (1) excretory ducts of sweat glands, (2) hair follicles and hairs, (3) structureless material, (4) empty spaces.

The mouths of the excretory ducts of sweat glands are surrounded by concentrically arranged layers of corneal cells and the cells lining the ducts are hornified on their course through the epidermis. In some of the ducts cornification of the epithelial cells may be observed for some distance into the cutis, this causing the formation of cylinders composed of concentric layers of cornified cells. Depending on the direction of the section and its relation to the lumen of the duct, various pictures may be produced, the lumina appearing circular, oblong, or irregularly compressed from the sides and assuming various forms. Frequently several excretory ducts are found in one system of concentric lamellae.

The mouths of hair follicles and of sebaceous glands are also surrounded by concentric layers. In the scalp the layers of horny cells in the stratum corneum run in every direction, but around the hair they are always concentrically arranged. The cornified cells invade the ducts of the hair follicles, but usually only to the mouths of the sebaceous glands, and cylinders similar to those seen in connection with the sweat glands are formed. In these cylinders hairs may have a straight or wavelike course. Wherever these cylinders lie close together the spaces between them are occupied by more or less solid horny lamellae, which are continuous and connect together the horny cylinders of the hairs. In places where the hair is more scanty, the sections of the horny cylinders are farther apart, and surrounding them and binding them together are massive layers of horny cells which usually show a wavelike stratification parallel to the papillary surface. Often several horny canals are so close together as to form a bundle. The direction of the cylinders is never vertical to the surface, but always markedly oblique, often almost horizontal.

Besides the systems of concentrically arranged lamellae enclosing ducts of sweat glands and hair follicles, concentric lamellae are seen enclosing deposits of a more or less homogenous mass. These deposits are of various shape and irregularly scattered throughout the stratum corneum. They have been seen by many observers, but there is a wide diversity of opinion as to the nature of the material enclosed

within the concentric rings of the lamellae. Moore and Warfield [20] regard the enclosed material as degenerated epidermal cells. Meyenburg regards these deposits as cell masses and enclosed masses of detritus. Jahn thinks that the contents of these enclosures is sebum and he states that he has found these accumulations both in the cutis and in the epidermis. Other authors (von Schab, Schabel, Stühlinger, Müller [21]) regard them also as products of sebaceous glands. Riecke, however, says that on the basis of his studies he believes that the possibility of these masses being secretion of sebaceous glands or fatty masses is entirely out of the question. He explains the development of these enclosures as follows: The cutis sends out projections into the horny deposits. The projections first become edematous, later completely degenerated and then changed into desiccated necrotic masses; the rete malpighii (stratum germinativum), becoming more and more slender, finally cornifies. Such enclosures may still remain connected with the processes of the cutis. Due to the direction of the section, however, they appear often as isolated enclosures. Moore and Warfield remark that some of these enclosures look not unlike the cell nests of epithelioma.

Concentric lamellae enclosing empty spaces in the corneal layer have been seen by Moore and Warfield. Riecke says that in a number of cases irregular, more or less slitlike interstices were observed in the corneal layer, which, however, have been found to be artefacts due to the shrinking of the tissue in alcohol.

It is remarkable how suddenly the hyperkeratosis stops at the muco-cutaneous junction. Moore and Warfield describe this striking phenomenon as follows: "In the section of the lip the mucous membrane on the buccal side is quite normal. On the exposed portion of the lip there is a small amount of horny material, which at the junction of the lips and of the skin suddenly becomes enormously thickened, having all the characteristics described above. The abrupt change is rather remarkable, as if there were an invisible barrier extending deeply into the skin, beyond which the disease process could not extend."

The tissue covering of the fissures intervening between the horny plates varies in its histologic structure. Some of the fissures have no epidermal covering, the cutis being directly exposed. From this one may conclude that these fissures are of so recent development that the epidermis has not had time to cover them. Other fissures possess epidermal covering which, however, in most cases is very thin and

---

20. Moore and Warfield: Fetal Ichthyosis: Report of a Case with Pathological Changes in the Thyroid Gland, Am. J. M. Sc. **131**:795, 1906.
21. Müller: Ichthyosis congenita, Verhandl. d. Phys.-med. Gesellsch. in Würzburg **1**:119, 1850.

devoid of hair follicles and glands, their rudiments being present occasionally. Riecke states that all the skin fissures that he has studied in two of his cases possessed epidermal covering. The horny layer of the fissures he found moderately thickened in its central portion, increasing in thickness laterally.

Statements of different authors vary as to the presence or absence of stratum lucidum. Riecke says: "in many pieces of the skin above the stratum granulosum a layer of horny cells corresponding to the stratum lucidum and composed of one to two rows of cells may be demonstrated, which in most stained specimens may be well differentiated by its lack of keratohyalin on the one hand and the vesicular nature of its cells on the other from the granular layer and the following layer of the massed horny cells. This layer, however, is not constant." Meyenburg states that the "stratum lucidum and stratum granulosum are united." Other authors, while not making any positive statements about the stratum lucidum, say that the stratum corneum is formed directly from the stratum germinativum (Unna, Moore and Warfield, etc.).

According to Riecke, the stratum granulosum is of normal thickness and the formation of keratohyalin, corresponding to the different regions of the body, shows only physiologic variations in intensity. Wassmuth was able to demonstrate the stratum granulosum in the scalp only. According to Meyenburg "stratum lucidum and stratum granulosum are united."

Riecke found no structural anomalies in the stratum germinativum. The epidermal covering of the fissures was thinner than in those regions of the skin that are covered by horny plates. Moore and Warfield are of the opinion that this layer is thinned. At a little distance from the fissures, the cells of the stratum germinativum were found to be small and compactly arranged. Very near the fissures, however, the cells of this layer were found to be larger, pale, separated from each other somewhat, and many mitotic figures were seen. They regard this as an effort on the part of nature to bridge over the gap. In no other places were mitotic figures seen in the stratum germinativum. Wassmuth says he found the stratum germinativum to be moderately thickened, the cells of the epithelial pegs assuming spindle form, but nearer to the surface becoming polygonal. Galewsky speaks of "new formation in the rete."

As to the condition of the dermis (cutis, true skin) the statements of authors vary considerably. It is said to be of normal thickness (Schabel, von Schab, Wassmuth) or generally thickened (Claus, Jahn, Stühlinger). Hypertrophy of the papillae was seen by many authors

(Bruck,[22] Claus, Jahn, Koller, Schabel, Straube [23]). Unna considers the papillary changes secondary to the hyperkeratosis.

The histologic structure of the dermis was found to be normal in almost all cases. Abundant accumulation of lymphoid and of round cells, combined with hyperemia and suggesting inflammation, were observed by Claus, Jahn, and Brandweiner.[24] Wassmuth states that he has found in the derma only an insignificant chronic inflammation of low grade. The blood vessels of the derma were found to be dilated by Bruck, Claus, Jahn, Lassar,[25] Koller, Straube, Bossert,[26] and of normal size and arrangement by Riecke. As compared with the normal skin, the papillae were much more numerous, broader and flatter, with greater irregularity in form and size (Riecke). Daniel and Cordes [27] state that the corium is edematous and contains less elastic tissue than normal, the papillae of the corium are hypertrophied, and their blood vessels are widely distended with blood. Riecke, on the other hand, states that wherever elastic tissue was studied, it was found to be normal. Moore and Warfield, however, make a statement that "in sections, stained with Weigert's elastic tissue stain the elastic fibers appear to be decreased in amount, and in many places are ruptured. . . . The true cutis is in most places normal in appearance. The papillae following the contour of the rete mucosae are in places elevated, but, on the whole, do not seem as large as normal. In some places there are collections of cells, lymphocytes and plasma cells, in great numbers, and it looks somewhat like embryonal connective tissue. The fat in all sections is decreased in amount. The leukocytes are few in number even where the skin is fissured. All the blood vessels are markedly congested, but are not thickened."

The subcutaneous fat tissue was well developed almost everywhere, although not excessive, in both of Riecke's cases. The blood vessels and nerves traversing this layer, showed no pathologic changes. It was found somewhat less developed by Claus, Firmin,[28] Koller, and found to be somewhat thicker by Gerstenberg.[29] According to Daniel

---

22. Bruck: Ein Fall von Ichthyosis congenita. Inaug. Diss., Berlin, 1888.

23. Straube: Ein Fall von Ichthyosis congenita. Inaug. Diss., Marburg, 1883.

24. Brandweiner: Die Hautkrankheiten des Kindesalters. Leipzig u. Wien, Franz Deuticke, 1910.

25. Lassar: Demonstration eines Präparates von sogenannter Ichthyosis congenita, Berl. klin. Wchnschr. **23**:836, 1886.

26. Bossert: Kasuistischer Beitrag zur Ichthyosis congenita. Jahrb. f. Kinderh. **82**:216, 1915.

27. Daniel and Cordes: Case of fetal ichthyosis, J. A. M. A. **35**:1081 (Oct. 27) 1900.

28. Firmin: Contribution à l'étude de l'ichyose foetale. Thèse, Paris, 1899.

29. Gerstenberg: Zur Pathologie der Ichthyosis congenita, Deutsch. Arch. f. klin. Med. **57**:263, 1896.

and Cordes, panniculus adiposus is everywhere poorly developed, being absent in places (due to prematurity).

There is a wide diversity of opinion among authors as to the condition of the sweat glands, and the statements vary from "entirely normal" to "total absence or atrophy." Carbone [30] and Riecke found them to be normal, except for the cornification of their ducts. Daniel and Cordes and Wassmuth state that they are increased in number, but otherwise normal. Claus and Stühlinger report that they found the sweat glands hypertrophied, while Straube reports their complete absence. Meyenburg says that there are no sweat glands in the skin of the body, but in the skin of the palms and soles they are increased in number. Koller found them absent, but he observed well developed excretory ducts in the palms and soles. Here the excretory ducts of the sweat glands present an especially characteristic appearance which was first described by Müller [21] and confirmed also by many other authors. He described their course as follows: "After they have risen in their ordinary spiral course for some distance, they assume a straight course and all of them bend so sharply to one side that they lie almost horizontally to the epidermis. Thus they approach the surface gradually and near the surface they become curved again. Thus ten to fifteen or even more straight horizontal canals are situated above each other and this causes the finely striated appearance of the epidermis." Riecke says that the sweat glands and their ducts were found to be normal with the exception of that portion of the duct which runs through the epidermis, this portion being enclosed in a horny cylinder described above. The number of the sweat glands he states to be normal, although some authors have reported an increase in number in palms and soles. This wrong statement, according to Riecke, is due either to the lack of knowledge of the normal conditions or to the fact that the excretory ducts, being enclosed in thick horny cylinders, appear to be close together. The cornification of the sweat gland ducts begins at their mouths on the surface of the epidermis and is present throughout the epidermis. In a few ducts the cornification proceeds down into the derma for a variable distance. Moore and Warfield state that the glandular cells of both varieties of glands (sweat and sebaceous) are seen to be swollen in places and seem to be undergoing some sort of degeneration, but never cornification.

Concerning the sebaceous glands, there is also a wide diversity of opinion. Caspary [31] and Straube report total absence of sebaceous glands in their cases, while Wassmuth found them to be increased in

30. Carbone: Un caso di ictiosi congenita. Arch. per le sc. med., **15**:349, 1891.

31. Caspary: Ueber Ichthyosis fetalis. Vrtljschr. f. Dermat. **13**:3, 1886.

number. The walls of their ducts are cornified or the mouths of the ducts are occluded by horny plugs (Bruck). Rudimentary development or even total atrophy has been observed by Müller, Claus, Gerstenberg, Jahn, Schabel and Stühlinger. In some of these cases, however, besides completely degenerated glands, other completely normal glands were seen. Irregularities in the course of the excretory ducts in the form of cylindrical or spindle shaped dilatations or thickenings are mentioned most frequently. The ducts were found partly well formed, partly with cystlike dilatations, or atrophied and with their secretion scanty and mostly retained.

In the hair follicles and the hair, conditions were found to be similar to those present in the sebaceous glands. Their under development or atrophy was reported by Gerstenberg, Koller, Kyber and Wassmuth. Markedly elongated hair follicles with dilated lumen and abundant fat contents were observed by Claus, thickened hair follicles by v. Schab. By the excessive thickness of the epidermis the development of the hair and especially of lanugo hair is frequently retarded and the hairs remain coiled down in the hair follicles. Root sheaths were found totally or partially cornified by Claus. Riecke states that the hair papilla and the lower third of the hair follicle, including its content, are normally developed in almost all instances. Only in places of especially extensive horny deposits, many hairs in their lowermost portions give an impression of light atrophy.

The main site of the changes, which consists of superimposed horny lamellae, either loose or adherent, is the hair funnel, and these pathologic formations in most cases reach to the mouths of sebaceous glands only. The hair funnels filled with horny masses are in some places enlarged. Peculiar is the behavior of the hairs in the fissures which intervene between the horny plates. The hairs are always so situated that they exert traction against the horny shields surrounding the fissures. On transverse section of the fissures they appear to diverge in both directions. "In one piece of the skin which contained a fissure dividing in the shape of a fork, enclosing horny shields, there was an instructive alteration in the direction of the hair and of the papillae. In both fissures the divergence of the papillae and of the hairs was very striking. In the horny plate lying between, the convergence of the papillae and of the hairs towards the middle was noted. This picture gives us a clew as to the time of beginning of cornification, since the horny armor seems to determine the direction of all the hairs present. The stiffness of the surface therefore must have appeared during embryonal life at a time when the rudiments of the hairs of this location have all developed" (Riecke). Esoff [32] describes hyperplastic lateral epithelial outgrowths of the hair follicles.

32. Esoff: Beitrag zur Lehre von der Ichthyosis und von den Epithelialwuchrungen bei dersselben nebst Bemerkungen über den Haarwechsel, Virch. Arch. f. path. Anat. **69**:417, 1877.

In general the various regions of the skin differ only in the degree of the changes. The quantity of the hair determines the formation of horny shields, and the horny deposits in densely haired regions appear to be sievelike. In the horny shields of the regions of the body covered by lanugo hair the wavelike layers prevail and the horny canals for the hairs are arranged in groups.

The horny deposits of those portions of the skin that possess no hair have a great resemblance to callous horny masses. They contain neither systems of interspaces due to the hair taking part in the process, nor the above described enclosures of necrotic portions of the tissues, the change being chiefly simple hyperkeratosis.

Thus the skin of the soles and of the palms shows some structural differences from the skin in other portions of the body. Some of these differences have been mentioned already. Stratum corneum is formed of numerous superimposed layers of horny plates. Stratum lucidum is indicated and stratum granulosum easily demonstrable. Stratum germinativum is normal. The dermis is normal, the papillae being only slightly developed, however. The coils of the sweat glands are everywhere well developed and form at the border of the subcutaneous tissue an almost continuous layer; their excretory ducts are normal. There are no enclosures.

The nail plate on the fingers is covered by a thick layer of horny lamellae. The nail bed and the nail plate are normal.

Riecke summarizes the characteristic histologic findings as excessive formation and accumulation of horny cells, enormously increased cornification in the hair funnels, slightly altered papillae, separation of portions of the cutis and their enclosure within the stratum corneum. Brandweiner says that "in less severe cases there are no essential differences from the picture as presented in ordinary ichthyosis."

As to the development of the pathologic condition of the skin, the majority of authors are of the opinion that the leather-like epidermal covering, because of the lack of elasticity, has become too narrow for the growing fetus and cracked in many places. Thus a number of fissures are formed which, because of the favorable condition of the skin surrounded by amniotic fluid, gradually became covered by the skin again. By continued traction the flattened down margins develop and due to the same cause is also the peculiar course of the ducts of the sweat glands on the hands and feet (Müller, Bruck, Jahn, Straube, von Schab).

Wassmuth attempted to explain the process by deficient or lacking desquamation of the superficial layers of the stratum corneum, which again is due to the epidermis not reaching complete cornification.

Besides pathologic alterations of the skin and skin appendages, pathologic changes were found also in other organs of the body. Those that may probably be regarded as secondary to the skin changes seem to be pretty constant, e. g., congestion of the internal organs, while those alterations that must be regarded as primary changes and having probably some bearing on the etiology of the condition, are somewhat inconstant.

Congestion of the internal organs so extensive as to bring about a picture of exudative inflammation in some cases was observed by many authors (Firmin, Daniel and Cordes, Riecke, Wassmuth, Gerstenberg, Moore and Warfield). Firmin makes an interesting remark that this congestion is analogous to the one found in individuals dying of extensive burns. In the case studied by Daniel and Cordes the kidneys showed lesions of acute exudative nephritis, in the liver there was granular degeneration of the hepatic cells and the meninges of the brain showed extensive hemorrhage, while other organs presented no pathologic changes save intense congestion.

Winfield[33] found total absence of the thyroid gland. Moore and Warfield found atrophy of the thyroid gland and of the thymus. They described the thyroid gland as follows:

Thyroid gland lies in the usual position and has an isthmus connecting the two lobes. The lateral lobes are about 13 mm. long, 6 mm. wide and 5 mm. thick. The gland is undoubtedly much smaller than normal, but in gross shows nothing striking, except the small size. It is, like all the organs, congested and at one spot there is a macroscopic hemorrhage within the gland.

Interesting and curious changes are seen in the gland, which have robbed it of all resemblance to the normal thyroid. In the sections of a normal thyroid of an 8 months, 40 cm. fetus we found a delicate framework of connective tissue, and alveoli lined with low cuboidal cells and filled with homogenous colloid. Sections of the thyroid in our case show none of the normal appearances. A glance at the specimen under a low power shows cellular collections separated from each other by dense bands of fibrous tissue. No typical alveoli are seen, but here and there open spaces, irregular in shape, which contain cells and granular material, and which have very little resemblance to the normal colloid. A mixture of desquamated cells and granular material has replaced the colloid substance. Instead of the symmetrical, mosaic-like appearance that the normal alveoli filled with colloid give to the gland, there is confusion and conglomeration. The alveoli are lined for the most part by columnar cells, having a small, round, deeply staining nucleus near the bases of the cells. A large cell with a large vesicular nucleus is also seen among the other cells in the alveolar wall. Both kinds of cells go to make up the alveoli, and are also found free in the centers of the alveoli. These cells in many places are seen to have undergone partial degeneration. The material in the alveoli in which the cast off cells lie, is granular and does not give the homogenous stain of normal colloid. There is no lining layer of cells in the sense used in speaking of normal alveoli. The two kinds of cells described above, which predominate in the cellular tissue, are mixed together in no regular arrangement. Some of

---

33. Winfield: A Contribution to the Etiology of Congenital Ichthyosis; Report of a Case with Absence of the Thyroid, with Microscopic Report of the Condition of the Skin, J. Cutan. Dis. **15**:516, 1887.

these so-called alveoli have been made to assume bizarre shapes by the ingrowth of the connective tissue in the wall, forming papillary processes that project into the spaces.

There is an enormous increase in the connective tissue, which shows both hyalin degeneration and young fresh fibers as evidenced by the fibroblasts seen in portions of the section. The rapidly growing fibrous tissue seems to be compressing the gland and causing it to atrophy. The increase of fibrous tissue, in the main, is seen where the large lobulations of the gland are formed, although fairly large strands are seen separating the smaller lobules.

The blood vessels are distended with blood, and at one spot in the gland there is considerable hemorrhage, apparently having come from a ruptured vessel. There is also thickening of the media, and adventitia but no calcification or atheroma.

The appearance of the gland is quite like the atrophic thyroid in sporadic cretinism, as described by Packard and Hand.[34]   They found thickened arterioles and calcareous degeneration.   It is interesting that nowhere, so far as we can find, are such changes noted in the thyroid gland, except in the two conditions above, and that cretinism, keratosis fetalis, and fetal athyrosis of pigs (Smith [35]) are characterized by marked cutaneous changes.   The coincidence is curious.   Thyroid administration has been tried in the treatment of ichthyosis (Fox [36]), and Nordman and Badet [37] report the cure of a case of congenital variety by the administration of thyroid.   In previously reported cases, the condition of the thyroid has received scant attention.   Huebschmann [38] reported findings similar to those of Moore and Warfield. In the only other case of fetal ichthyosis where examination of the thyroid is specifically mentioned (Daniel and Cordes) it was said to be normal macroscopically and microscopically.

Lesions of congenital syphilis were never found in this condition. Gerstenberg, who regards keratosis diffusa fetalis as a trophoneurosis, found striking pictures of interstitial neuritis in the brachial plexus.

It is of considerable importance that, while most of the patients die even in the absence of complication, no pathologic changes were found that could be designated as the ultimate cause of death and the question as to what causes death in these cases has not yet been answered.   It is certainly not inanition, because even those that were fed by catheter died.   It seems rather to be due to deficiency in the

34. Packard and Hand: A Contribution to the Pathological Anatomy of Sporadic Cretinism, Am. J. M. Sc. **122**:289, 1901.

35. Smith: Fetal Athyrosis. A Study of the Iodin Requirements of the Pregnant Cow, J. Biol. Chem. **29**:226, 1917.

36. Fox: Ichthyosis in a Child Aged 16 Months, Treated by Thyroid Extract, Proc. Roy. Soc. Med., London **4**:72, 1910.

37. Nordman et Badet: Ichthyose congénitale, guérie par le traitment thyroidien, Loire méd. **29**:459, 1910.

38. Huebschmann: Ueber Ichthyosis congenita. Arb. a. d. Geb. d. path. Anat. u. Bakt., **6**:500, 1908.

function of the skin, to prematurity (which is the rule) and to deficient constitution. In a few cases which died shortly after birth pneumonia was present.

REPORT OF CASE

Clinical History.—The child was admitted to the Sarah Morris Hospital for Children when one day old. The external surface of the body showed the condition described in the necropsy report. Birth was normal, at the end of a normal full term pregnancy. The mother had had no miscarriages. Two previous children were normal. The mother has had eczema for many years. Her blood Wassermann was negative. The child was catheter fed with breast milk after admission, but appeared to be weak and had difficulty in swallowing. Death occured on the eighth day after birth.

Necropsy Report (abstract of report by Dr. I. Perlstein).—This is the body of an undersized child which is 43 cm. long and weighs 1,575 gm. The skin presents changes due to perverted keratinization. The integument is thickened and hardened, split up into plates and scales by rents and fissures of various depth and width (Fig. 1). The general color is grayish or yellowish. The skin is hard and leathery to touch. The epidermis plates are of various shape and size (Fig. 2). They are mostly angular. Some are round. They are smallest where the most movements occur, as in the groins, popliteal spaces, axillae, etc. They are largest on the scalp and on the back (Fig. 3). The hands and feet are edematous, small and covered by smooth glistening skin (Figs. 4 and 5). They are atrophic and the joints are ankylosed. The nails of hands and feet are poorly developed. The eyes are small, slitlike and deeply seated due to edema of the eyelids, which are also covered by horny plates. Eyelashes and eyebrows are not seen. No hair is to be seen anywhere upon the surface of the body except in the occipital region of the scalp, where a narrow fringe of fine, sparse, short, light colored hair is present. The mouth is open and gaping, and has the appearance of that of a fish (Fig. 6). It is surrounded by plates and rhagades which produce a contraction of the soft parts. The nose appears flat and small because the depressions around it are filled up by thickened skin. The auricles are not visible, since they are covered by epidermic plates which also occlude the external auricular meatus. The external genitals are small and covered by epidermis plates.

The body is opened by the usual longitudinal incision. There is a very thin subcutaneous layer of fat. The peritoneal and thoracic cavities have smooth and glistening serous surfaces and contain the usual amount of moisture. The thoracic and abdominal organs are in normal relation to each other. They are removed in toto including the tongue and organs of the neck.

The internal organs, except the lungs, show nothing of note except congestion. The right lung weighs 40 grams and is covered in places by a small amount of fibrin. The upper lobe is completely consolidated and the two lower lobes are consolidated in the posterior portions. These parts are dark red and fleshy in color and sink in water. Left lung: The upper lobe has a small dark red, hard patch which measures 2 cm. in diameter, the lower lobe has three areas of the same kind, which are somewhat smaller. The testes and glands of internal secretion are normal, with the exception of the thyroid. The latter nearly encircles the trachea. It has a right and left lobe connected by a thick isthmus. It weighs 5 gm. The left lobe measures 2 x 1.3 x 1 cm.; the right, 1.8 x 1.1 x 1 cm. The isthmus measures 0.7 cm. between lobes, 1 cm. from superior to inferior margin, and 3 mm. in thickness. The left thyroid at its upper posterior pole, at the junction with the isthmus, contains just beneath the capsule two pale areas each 5 mm. x 3 mm., separated from each other by a very narrow strip of darker tissue. The right lobe at the same situation contains an area of similar tissue. At the middle of the outer lateral aspect of the left thyroid is a pale subcapsular area 2 mm. in diameter.

Anatomic diagnosis: Congenital hyperkeratosis; acute lobar pneumonia.

With the exception of the lungs, thyroid and skin, the microscopic examination shows nothing, except extreme congestion.

Lung: In the unconsolidated portion of the lung tissue the alveoli vary in size. The septums are thick and contain many oval, rather deeply stained nuclei, together with a few lymphocytes. Some of the smaller alveoli are completely filled by swollen, desquamated epithelium. In the consolidated tissue, which is rather sharply delimited from that which contains air, the original lung structure is recognizable with difficulty. Many alveoli are densely filled with red blood corpuscles. Other areas are more cellular, the alveoli being packed with desquamated epithelia, lymphocytes and pus cells. While polynuclear leukocytes are numerous in places, in general the lymphocyte is the predominating cell type. In the consolidated tissue are several clumps of bacteria, some definitely within small blood vessels.

Thyroid: In sections including the entire right lobe, the thyroid nature of the tissue is nonrecognizable except in a small narrow subcapsular zone. The rest of the tissue is subdivided into lobules of varying size by bands of fibrous tissue of varying thickness (Fig. 7). The stroma carries numerous blood vessels which are markedly distended with blood. The lobules are composed of closely placed round and oval cells which show no follicular arrangement and no lumen formation. In their appearance the lobules suggest lymphoid rather than thyroid tissue. The cells have nuclei which vary in size from that of the nucleus of a small lymphocyte to that of a large unripe lymphocyte. The small nuclei are dense and deeply stained, the larger ones somewhat more vesicular. The nucleus is surrounded by a relatively large amount of homogenous eosin stained cytoplasm. The larger cells measure up to 18 microns in diameter and have nuclei up to 10 microns in diameter. The smaller cells average 13 microns and have nuclei 6.6 microns in diameter. In a relatively small subcapsular area of thyroid tissue, follicles are present in the lobules (Fig. 8). The follicles vary in diameter from 70 to 220 microns, only a few being of the latter size, the average about 100 microns in diameter. The follicles are lined by a single layer of low cuboidal epithelium, with nuclei small and condensed and of the same size and appearance as the smaller nuclei in those portions of the gland where no follicles are present. The lumens of the follicles contain deeply eosin stained, normal appearing colloid. The surface area of the entire section is 80 sq. mm.; that of the differentiated area 13.5 sq. mm. The pale areas noted in the gross description of the left lobe are similar small islands of differentiated thyroid tissue. Only in the four small areas noted, namely at the upper poles of the two lobes, and on the lateral aspect of the left lobe, does the thyroid show its normally differentiated structure and in these areas only the most superficial subcapsular zone is differentiated.

Skin: Sections were taken from the back, the abdomen and the scalp, where the keratosis was very marked; from the leg, where the thickening was only slight; from the sole of the foot in an area which showed no macroscopic keratosis; from the thin smooth skin of the great toe; from the margin of the eyelid and from the lip.

Skin of the back: The section includes one of the broader furrows with some of the markedly thickened skin on each side. In the latter situation the free surface is covered by a markedly thick, horny layer, most of which is in finely laminated, whorllike areas, the majority of which have a clear space or opening in the center. A few groups of small compressed and condensed nuclei are scattered about in the horny material, usually in that which lies between the whorls. The upper surface of the epidermis itself is very irregular, projections caused by broad, flat topped papillary structures alternating with depressed areas of about the same width. The projections are formed by three to as many as eight slender, long, dermal papillae covered by and separated from each other by epidermis (Fig. 9). In the depressed areas between the

projections the papillae are short and thick. The epidermis is very thin. The lowermost cells are cuboidal and are not so high or so regularly arranged as the normal malpighian layer. Above this is a layer which is from two to four cells thick over the summits of the papillae (Fig. 10) and which appears to correspond to the stratum spinosum. The cells, however, are very closely placed and show no intercellular bridges. Above this is a layer of about equal thickness, the nuclei of which are slightly more widely separated and lie in a dense, deeply eosin stained matrix. This layer appears to correspond to the stratum granulosum, but individual cell outlines are not distinguishable and the layer contains no granules except in a few small widely separated areas. Above this comes a nonnucleated layer about equal in thickness to the rest of the epidermis, composed of very thin lamellae arranged parallel to the surface of the epidermis. The deeper half of this area takes a purple tinge, due to the presence of numerous very minute blue staining granules and corresponds apparently to the stratum lucidum. The superficial half of this zone is free of granules, has the appearance of closely laminated stratum corneum, and goes over superficially into the thick whorl-like horny material described.

The cutis vera contains many spindle nuclei and a few lymphocytes. Hair follicles in the deeper cutis are few in number and widely separated, but just beneath the epidermis they are more numerous. These superficial follicles do not extend down much below the level of the deepest portion of the interpapillary epithelial down growths of the epidermis, their diameter is two to several times greater than normal, and they appear to take part in bringing about the irregularity of the epidermis. The widely separated follicles in the deeper tissue are smaller in diameter. Hornified material extends down into the hair funnels and into the follicles, the change being present even in the smaller deeper follicles, each of which contains a hyalin, homogenous, deeply eosin stained center, which at its middle point contains a small clear area. In most of the follicles a few cells of the stratum granulosum type are present. No normal sebaceous glands are seen, but about an occasional deep follicle are one to three atrophic compressed glandlike structures which look more like sweat glands than like sebaceous glands. Normal coiled sweat glands are also absent, but straight cellular strands, apparently compressed sweat ducts, lie widely separated in the cutis. The direction of these and of the hairs is such that they make a very acute angle with the epidermis, often running almost parallel to the latter in their course through the cutis. The blood vessels of the papillae and of the rest of the skin are markedly engorged. In the deeper layer of the cutis, just above the thin layer of fetal, not fully differentiated subcutaneous fat, the connective tissue bundles are widely separated by clear spaces of varying size, evidently the result of edema.

In the furrow the very thick whorllike horny layer is absent (Fig. 11). The epidermis here is covered by a thin horny layer about equal in thickness to that at the sides of the furrow. The epidermis, which here does not show the papilla-like irregularity of the thicker skin, is atrophic. The papillae are widely separated and they are very short and blunt. The normal stratification of the epidermis is not apparent. Above the cellular layer, corresponding apparently to the stratum spinosum, is a laminated layer which contains small, slender, compressed, very deeply stained nuclei lying in a hyalin matrix. Above this in turn is the horny layer. The tissue immediately beneath the epidermis contains many young connective tissue nuclei and a few lymphocytes and the blood vessels are markedly distended. Deeper down the stroma is edematous. Hair follicles are fewer in number than in the neighboring thickened skin and no sebaceous glands are recognizable. The sweat glands have the same atrophic appearance as those beneath the thickened skin.

The walls of the larger arteries and veins show no abnormality and the nerve trunks present also appear normal.

The skin of the abdomen shows the same condition as that of the back. In skin from the leg the same changes are present, but hair follicles are more numerous and the whorllike horny layer is not so thick as on the back. The hair follicles are here, as elsewhere, centrally hornified.

Scalp: In sections of the scalp taken from that portion which showed in the gross a fine growth of hair, the epidermis with its markedly hypertrophied whorled horny layer is three to four mm. thick. The epidermis has lost almost entirely its cellular character and has been transformed into keratohyalin lamellae. The stratum malpighii consists of an incomplete layer of cuboidal cells with small, deeply stained nuclei. In many places these cells constitute the only epidermal cellular elements left. In other places, there are superficially to this layer, a few cells, in general of the stratum spinosum type but without prickles and with nuclei which stain faintly, some of which appear edematous, others of which appear to have lost both fluid and chromatin. The papillae are very long and slender (Fig. 12) and they are arranged in groups of two or more, so that the upper surface of the epidermis has the irregular papillary character noted in the skin elsewhere. The stroma of the papillae is so edematous that it has the structure of mucoid connective tissue. In the latter lie blood filled small vessels and larger empty endothelial lined spaces, the latter apparently lymphatics. The hair follicles which here are fairly numerous are cut tangentially and transversely, indicating their oblique course through the tissue. Lying beside some of the follicles are atrophic sebaceous glands. Almost every follicle is accompanied by a well developed bundle of muscle. Sweat glands are very few in number, widely separated and atrophic.

Skin of the Sole: Of the skin from various areas examined, that of the sole of the foot is nearest normal. The horny layer, while about twice the thickness of the rest of the epidermis and its papillae, does not show the whorllike arrangement which is so striking elsewhere. Its closely placed lamellae are regularly arranged, run parallel to the surface of the epidermis and contain a slight amount of finely granular blue stained material. Granulosum and lucidum layers are not present, the stratum spinosum going over directly into a layer from five to eight cells thick, in which the nuclei are small and condensed and the cytoplasm dense, hyalin and without extranuclear chromatin. This layer goes over sharply into the stratum corneum, which contains no nuclei but does contain, as already noted, scattered fine chromatin dust. The papillae are long, slender and closely placed. Just beneath the papillae the stroma contains many spindle nuclei and a few lymphocytes. Sweat glands are numerous, closely placed and normal in appearance. Their ducts, cut obliquely and transversely, form numerous cellular strands and islands in the stroma beneath the epidermis. No hair follicles or sebaceous glands are present. The thin glistening skin of the toe has the same structure as that of the sole except that the papillae are not so long, slender and closely placed and the numerous sweat glands and ducts are absent.

In order to determine whether the changes described are limited to the covering epidermis, sections were taken from areas other than the skin which normally are covered by squamous epithelium and from places where the epidermis goes over into nonhornified epithelium. The squamous epithelium of the upper esophagus is normal. That of the tongue likewise shows none of the changes noted in the epidermis. Just at the tip of the tongue a thin superficial layer of the epithelium is more hyalin than normal and its nuclei are condensed. This change is apparently due to drying, the result of the constantly open condition of the mouth. The papillae at the tip of the tongue contain many young fibroblast nuclei and the vessels are engorged. The deeper structures show no abnormality. The epidermis of the outer surface of the eyelid shows the same hyperkeratosis and the same hornification of hair follicles as the rest of the epidermis, the atrophy and irregularity of the epidermis itself are not so marked, and normal sebaceous glands are more numerous here than elsewhere. At the lower margin of the eyelid the hypertrophied horny layer

ceases very abruptly. The epidermis here is thin. On the inner surface of the lid the squamous epithelium is desquamated in numerous small areas. In a section through the lower lip the epidermis is more nearly normal than elsewhere. All the normal epidermal layers are distinguishable here, a condition not noted in skin from any other area examined. Many of the cells of the prickle layer are vacuolated. The surface is covered by a thin horny layer whose lamellae, which run parallel to the surface, contain a few shrunken compressed nuclei. The hair follicles are long, run at right angles to the surface, are centrally hyalinized and each has a normal sebaceous gland. The hair containing skin of the lip goes over very sharply into the hair-free epidermis of the scarlet portion of the lip. The latter appears normal. It is covered by a thin regular stratum corneum.

Elastic tissue of the skin: Sections from different areas were stained with Verhoeff's elastic tissue stain. The skin of the foot, which in the hematoxylin and eosin stain preparations shows little deviation from the normal, except moderate epidermal hypertrophy, contains many elastic fibrils arranged in the normal manner. In situations where the horny layer is markedly thickened and the epidermis atrophied, the elastic fibrils have largely disappeared. Those elements which can still be recognized occur as short, markedly tortuous and in places swollen fibrils and as rows of fine granules. In the deep subcutaneous tissue just above the muscle the elastic fibers are normally preserved. Where the skin is markedly furrowed, the elastic tissue shows very interesting relationships. At the margins of the furrows beneath the thickened skin the fibrils are absent or degenerated as described, whereas beneath the furrow, which is covered by a relatively thin regular horny layer, the elastic tissue is larger in amount and more normal in arrangement and appearance.

No treponemas are seen in sections of the various tissues and organs prepared by the Levaditi method. The placenta and umbilical cord are normal microscopically and contain no treponemas in Levaditi preparations.

DISCUSSION

The pathology of the skin has been given in detail, because from the study of the changes in this typical and marked case, conclusions have been reached in regard to the pathogenesis of the hyperkeratotic condition which are somewhat at variance with those of previous writers.

Bossert considers the condition one of abnormal hornification of hair follicles and skin, associated with abnormality in the course of the hairs. The latter he appears to regard a fundamental condition. Meyenburg finds thickening of the horny layer to be the one constant feature in all descriptions of the process, changes in the cellular epidermis being less uniformly noted. In his case there was no hair anlage, hence Bossert's idea of the importance of hornification of hair funnels and obliquity of hairs does not appear to hold. The oblique course of the sebaceous gland ducts in his case Meyenburg holds to have been brought about mechanically by tension of the elastic fibrils at the bottoms of the fissures. Schabel and Stühlinger believe that incomplete transformation of the epithelial cells of the sebaceous glands into fat prevents the normal formation of vernix caseosa. The incompletely transformed materials are retained and lead to the formation

of horny plates and shields. Wassmuth considers deficient desquamation, due to incomplete and abnormal hornification, the essential factor. Riecke concludes that the process is one of excessive formation and accumulation of horny cells, a conclusion which Esoff had reached many years previously, but he offers no explanation of how this process is brought about. He excludes the formative part of the skin from any part in the process, stating that the changes in the deeper epidermal layers lie within the limit of normal and that the process has no effect on the production of papillae. That Gerstenberg considers the process a trophoneurosis has been mentioned. Moore and Warfield suggest that absence of the thyroid, noted in their case, may be a factor in the persistence of the epitrichial layer of the epidermis. Unna places the condition among the stagmatory tumors due to progressive disturbance of nutrition, under the malformations of the skin. He defines it as a congenital excessive firmness of the whole horny layer, whose essential feature is a firmer connection of the epithelium. Papillarly changes he holds to be secondary to the influence of the hyperkeratosis on the rapidly proliferating embryonic prickle layer.

In the case here described the abnormal development of the horny layer, which is the most striking feature of the condition, is marked, and the hairs and the excretory ducts of the sweat glands take the very oblique course noted by others. But there are in addition other changes which are considered more fundamental. The absence of granulosum and lucidum layers in the epidermis indicates that the condition is not simply one of abnormal cornification, but that there is at work some interference with that process which normally transforms the epidermal cells of the deepest layer into the horny scales of the superficial layer through a definite and regular sequence of changes. Associated with the alterations in the epidermis itself are hypertrophy of the dermal papillae in most situations, a condition especially marked in the scalp where hyperplasia of the horny layer is extreme, and atrophy of papillae in other areas. The cutis throughout is the seat of slight subacute inflammatory reaction, as is indicated by the presence of moderate numbers of lymphocytes and by the increase in young spindle nuclei. Hair follicles in general are much less numerous than normal and all show central cornification. Sebaceous glands are absent, or where present they are undergoing atrophy. The sweat glands are decreased in number, except in the skin of the sole, and those present are compressed or are undergoing atrophy.

It is inconceivable that the very thick stratum corneum which is present could be the result merely of abnormal hornification or of failure of normal desquamation during fetal life. Such an amount of

horny material could not be formed except from pre-existing epidermal cells. The latter could not be formed in numbers sufficient to produce such a thick stratum corneum unless there had been a previous stage of epidermal hypertrophy and hyperplasia. Evidences of such hypertrophy are present in the skin examined. In the sole of the foot, where hyperkeratosis is slight, the papillae are long, numerous and closely placed, and sweat glands are numerous. Where hyperkeratosis is most marked many of the papillae are still abnormally long, while others are short and atrophic. The interpretation of the changes noted in this case is that the primary condition was one of hypertrophy of the skin and that the hypertrophy led to an increase in the stratum corneum. Hypertrophy was followed by atrophy, a condition evidenced by the thinning of the cellular portion of the epidermis and by the disappearance of stratum granulosum and stratum lucidum; by flattening and loss of dermal papillae; by disappearance of hair follicles, sebaceous glands, and sweat glands, and by disappearance of elastic tissue.

The fissuring of the epidermis, the obliquity of the hairs and skin glands, and the deformity of the face and of the terminal phalanges of the fingers and toes are changes secondary to the atrophy. Irregularity in the disappearance of the elastic tissue during the stage of atrophy leads to irregular contraction of the skin, with the formation of fissures. At the same time, it leads to more or less general retraction of the skin, so that the phalanges become permanently flexed, deformed, and hindered in their further development. The oblique course of the hairs and of the skin glands is likewise due to this dislocation of the skin and appears to be purely mechanical.

The explanation of the causation of the series of changes described is another and more difficult matter. Because of the alterations which occur in the skin in conditions of loss of thyroid function, it would seem pertinent to consider the possibility of relationship of abnormality of thyroid function to keratosis diffusa fetalis. Absence of or failure of development of the thyroid has been noted by Winfield and by Moore and Warfield. In Wassmuth's case the parents were high-grade cretins. In Moore and Warfield's case the thymus was atrophic and fibrous. In our case the thymus shows no striking deviation from normal, except richness in Hassall's corpuscles, but the thyroid gives definite morphologic evidence of loss or absence of function. With the exception of four small, and relatively insignificant areas, the thyroid is totally undifferentiated. It is composed of small cells without any follicular arrangement and with no formation of secretory material, except in the small islands noted. In general, the abnormality of the thyroid in this case appears to be of the same nature as that

noted by Moore and Warfield in their case. (Compare their Figure 4 with our Figure 7.) Unfortunately, their illustrations are not accompanied by legends or by direct references in the text, so that it is impossible to decide whether their Figure 5 is an illustration of normal fetal thyroid which they studied or part of the thyroid from their case of keratosis fetalis. If the latter is the case their Figure 5 would be duplicated by our Figure 8, from one of the small differentiated areas of thyroid tissue. The condition of the thyroid is striking and suggestive, but thyroid deficiency cannot be considered an essential factor in keratosis diffusa fetalis unless it occurs more frequently or more uniformly than the previous literature indicates. None of the other glands of internal secretion showed any deviation from normal which might be held to have any relation to the general condition.

SUMMARY

The case reported is an extreme and typical example of the condition under consideration. Thickening of the horny layer is marked. The hyperkeratosis is limited to those portions of the skin which normally develop a stratum corneum, and ceases sharply at those situations where the normal stratified horny epithelium goes over into nonhornified epithelium.

Associated with the abnormal keratinization are obliquity of the course of the hair follicles and of the skin glands, fissuring of the epidermis, and deformities and failures of development of the phlanges and of the face.

Evidences of papillary hypertrophy are present. The condition is considered to be primarily one of skin hypertrophy, which leads to an increased formation of epidermal horny material.

In the fully developed condition, atrophy of the skin is more prominent than hypertrophy, except in so far as the horny layer is concerned. The dermal papillae become shorter, flatter and less closely placed. Hairs, sebaceous glands, and sweat glands disappear, and there is a decrease in elastic tissue, the latter element remaining present in largest amount beneath the fissured areas.

The fissuring of the epidermis and the deformities of the extremities and other portions of the body are held to be secondary to the atrophic changes, being brought about by retraction of the skin.

With the exception of the thyroid and the lungs, the internal organs are negative, except for the marked congestion present.

The thyroid is undifferentiated and morphologically nonfunctioning. Deficient thyroid function during the developmental period may be a factor in the condition.

The condition has reached such an extreme degree of development by the time of birth as has been found to be incompatible with life in other cases. In this case pneumonia was the immediate cause of death.

<div align="center">CONCLUSIONS</div>

For the condition reported in the literature under the name ichthyosis congenita and a variety of other terms, which are based on some superficial gross anatomic peculiarity of the skin, the designation keratosis diffusa fetalis, based on the pathologic condition common to all the cases, is proposed.

The reported cases fall into three groups. In the first, to which the case here reported belongs, the abnormality is so extreme at birth as to be incompatible with a duration of life of more than a few days. In the second group, keratosis diffusa fetalis mitior, the condition is present at birth, but is not developed to so extreme a degree as in the first group. The duration of life depends on the rate at which the condition develops after birth and on the degree to which it develops. In the third group, keratosis diffusa fetalis tarda, evidences of the skin anomaly may not be present at birth. They develop after a period of variable length, and the degree of development which they reach is also variable.

Keratosis diffusa fetalis is a condition, having its origin in the fetal period of development, the most striking feature of which is marked increase in the horny layer of the epidermis and abnormal hornification of the epithelial skin structures.

The hyperkeratosis, which becomes the predominating element in the pathologic process, is believed to be the result of a preceding stage of hypertrophy and hyperplasia of the skin.

Absence of the thyroid or deficiency of thyroid function during intrauterine life may be a factor in the causation of the epidermal changes which characterize keratosis fetalis.[39]

---

39. The following references may also be consulted:

Bowman: Ichthyosis Fetalis Mitior, Med. J. Australia **1**:541, 1918.

Cabot: A Case of Ichthyosis Congenita with Some Unusual Features, Med. Rec. **48**:10, 1895.

Cohn: Ueber Ichthyosis atypica. Dermat. Centralbl. **17**:229, 1913.

Ehrmann: Zwei Fälle von Ichthyosis congenita bei Geschwistern, Arch. f. Dermat. u. Syph. **98**:110, 1906.

Galewsky: Ueber Erythrodermia congenitalis inchthyosiformis, Arch. f. Dermat. u. Syph. **113**:373, 1912.

Gandinin: Ichthiosis famigliare congenita; contributio alla eredarieta de l'ichthiosida una famiglia, Riv. di clin. ped. **10**:798, 1912.

Gassmann: Histologische und klinische Untersuchungen über Ichthyosis und ichthyosisähnliche Krankheiten. Ergänzungsheft z. Arch. f. Dermat. u. Syph., W. Brunmüller, Wien, 1904.

Goffe: Four Cases of Ichthyosis in a Family of Six Children. Two Cases of Ichthyosis in a Family of Five Children, Proc. Roy. Soc. Med., London **8**:63, 1914.

Humbert: Contribution à l'étude de l'ichtyose foetale. Thèse, Genève, 1906.

Litchfield: A case of harlequin fetus. Med. J. Australia **1**:494, 1918.

Martinotti: Sull 'ithiosi fetale, Gior. ital. d. mal. ven. **46**:88, 1911.

Mouriquand et Weill: Ichthyose et corps thyroids; présentation d'un myxoedémateux atteint d'ichthose améliorée par le traitment thyroidien, Lyon méd. **114**:288, 1910.

Rille: Ichthyosis serpentina. Deutsch. med. Wchnschr. **64**:1038, 1914.

Schwartz: Ichthyosis congenita. Bull. Lying-in Hosp. **6**:172, 1909.

Tomassi: Osservazioni sopre duo casi ittiosis familiare, Gior. ital. d. mal. ven. **67**:704, 1912.

Unger: Ein Fall von Ichthyosis congenita s. fetalis. Mitt. d. Gesellsch. f. inn. Med. u. Kinderheilk. in Wien **13**:239, 1914.

STUDIES ON THE INORGANIC CONSTITUENTS OF MILK*

WARREN R. SISSON, M.D., AND W. DENIS, PH.D.

BOSTON

I. CHLORIDS IN HUMAN MILK

In discussions of the composition of human milk and of modifications of cow's milk, much stress is laid on the absolute and relative proportions of fats, carbohydrates and protein, but, as a rule, no mention is made of the concentration of the mineral constituents. As an example, we may cite the fact that in many clinics the most premature infant is given mixtures of whey, which may provide certain advantages in regard to the quality of the protein, but which contain 300 per cent. more chlorids than does human milk. A similar relation exists in connection with several of the other inorganic constituents.

This practice is, of course, based on the assumption that an excess of inorganic material is present even in human milk, and that this excess is not injurious, an assumption not based on experimental evidence. Theoretically, it is, of course, perfectly conceivable that such an excess of salts may not only increase the work of the kidneys to a dangerous degree, but may even induce intestinal disturbances.

Stimulated by recent work which has demonstrated the importance of the mineral elements of the diet, we began about one year ago a study of the mineral constituents of human milk and of the various modifications of cow's milk ordinarily used in infant feeding.

In this paper, which is the first of a series dealing with this subject, we shall consider only findings on the chlorids of human milk.

METHOD OF ANALYSIS

Before attempting the collection of data, it was first necessary to find an analytical method by means of which it would be possible to obtain accurate results with a moderate outlay of time, and with relatively small amounts of material. Most of the milk chlorid determinations recorded in the literature were made either by gravimetric methods, usually from the weight of silver chlorid, or by the Volhard titration. In either case, a considerable volume of milk had to be evaporated to dryness, ashed in a platinum dish at low heat with the

help of an alkaline fusion mixture, and the ash then extracted with water. Such a process was tedious and time consuming, and one requiring an elaborate equipment and considerable chemical experience. The micro methods, which during the past ten years have been applied so extensively to the chemical study of the blood, can be used, in many cases, with slight modifications for the examination of milk.

Two methods for the determination of chlorids in blood are in current use, namely, Rappelye's [1] modification of the Volhard titration, and the iodonitric titration of McLean and Van Slyke.[2]

An attempt to utilize Rappelye's modified Volhard titration was unsuccessful because we were unable by means of it to obtain complete precipitations of the milk protein. We, therefore, have made use of the McLean-Van Slyke technic, with a few modifications made necessary by the nature of our problem.

Attempts to employ the Van Slyke-Donleavy [3] modifications, which involve the use of picric acid as a protein precipitant in place of the magnesium sulphate-acetic acid mixture of the original method, were unsuccessful, as it was found impossible also to obtain complete precipitation of the milk proteins in human milk by this technic. It was found, however, that if the proteins were first precipitated by means of a saturated solution of picric acid containing a little acetic acid and the acid silver nitrate solution then added without preliminary filtration, a clear filtrate could almost invariably be obtained.

In view of the fact that human milk contains only one-tenth as much chlorin as blood, it was necessary to make a few changes in the quantity and concentrations of the reagents. Although no claim for originality is made in this connection, it has seemed wise to furnish a brief description of our technic.

The titration as used by us, is as follows: To 3 c.c. of human milk contained in a 100 c.c. Erlenmeyer flask is added 9 c.c. of a 1.2 per cent. solution of picric acid containing 2 c.c. of glacial acetic acid per liter. After the mixture has stood for five minutes, 3 c.c. of the standard nitrate-nitric acid solution is added. After ten minutes the liquid is poured on a chlorid free filter. To 10 c.c. of the clear filtrate is added 2 c.c. of the starch indicator, and the excess of silver is then titrated by means of standard potassium iodid solution.

As it seemed best in this work to express our results in terms of milligrams of chlorin per 100 c.c. of milk, we have, in order to avoid the use of a factor, made a slight change in the concentrations of the

1. Rappelye, W. C.: J. Biol. Chem. **25**:509, 1918.
2. McLean, F. C., and Van Slyke, D. D.: J. Am. Chem. Soc. **37**:1128, 1915.
3. Van Slyke, D. D., and Donleavy, J. J.: J. Biol. Chem. **37**:551, 1919.

standard silver nitrate and standard potassium iodid solutions pre-
scribed by McLean and Van Slyke.

Solution 1

Silver nitrate .... 4.780 gm.
Nitric acid, sp. gr., 1.42......................... 250. c.c.
Distilled water, add to.........................1,000 c.c.

One c.c. of this solution is equivalent to 1 mg. chlorin.

Solution 2

Potassium iodid .... 1.5 gm.
Water, add to...................................1,000. c.c.

This solution is standardized against the silver nitrate and so diluted that
20 c.c. are equivalent to 5 c.c. of the silver solution.

Solution 3

This consists of a solution of starch, sodium citrate and sodium nitrate
made up according to the directions of Van Slyke and Donleavy.

It has recently been shown by Austin and Van Slyke [4] that the
Van Slyke-Donleavy procedure, when used on whole blood, gives results
greatly in excess of the truth. To remedy this they suggest the pre-
liminary precipitation of proteins by means of picric acid, and the
removal of the precipitate so obtained before the addition of the stand-
ard silver nitrate solution. Although our work on the subject had been
concluded before the publication of this paper, we have made a few
determinations by this method, and have, by means of it, obtained
results essentially similar to those obtained by the technic described
above.

TABLE 1.—Comparison of Results Obtained by Coagulation
and by Fusion Methods

Sample	Source	Mg. Chlorin by Coagulation	Per 100 C.c. Milk by Fusion
1	Human.................................	75	77
2	Human.................................	81	82
3	Human.................................	32	35
4	Human.................................	47	47
5	Goat..................................	165	165

The corrections of our results have also been checked by means of
Volhard titration used after the removal of the organic material by
means of fusion with sodium carbonate.[5] In Table 1 a comparison of
the results of determinations of the chlorin content of six samples of
milk made by coagulation and fusion methods is shown.

---

4. Austin, J. H., and Van Slyke, D. D.: J. Biol. Chem. **41**:345, 1920.
5. Bull. 107 (revised), U. S. Dept. Agriculture.

METHOD OF COLLECTION OF SPECIMENS

The specimens were collected by expressing the milk manually from the nipple into specially washed bottles. A breast pump was used in some instances, and it was found that the mechanical stimulation produced by this process caused no change in the chlorin content of the secretion. The nipples were carefully washed with water before collections were made and the use of boric acid and similar solutions was avoided.

The specimens were obtained in most instances about three minutes after the beginning of nursing, when the flow of milk had been established.

TABLE 2.—SHOWING CHLORIN CONTENT OF "FORE" AND "AFTER" MILK FROM NORMAL WOMEN

Number	Mg. Chlorin in "Fore" Milk	Mg. Chlorin in "After" Milk	Period of Lactation, Weeks
21–22	53.0	64.0	1
23–24	92.0	61.0	1
25–26	25.9	34.0	2
27–28	48.3	32.7	1
29–30	71.0	74.5	1
31–32	14.1	42.0	2
33–34	43.0	34.0	2
35–36	107.0	96.6	1
45–46	59.0	50.0	7
52–53	93.0	10.2	7
62–63	72.0	10.2	2
86–87	40.0	54.0	30
102–103	76.5	40.6	1
127–128	42.0	42.0	3
316–317	40.8	36.0	9
318–319	36.0	35.0	9
320–321	37.8	37.8	9
322–323	41.4	38.4	9
312–313	29.4	30.0	52
314–315	36.0	28.8	52
177–178	22.9	29.8	17
-168–169	75.0	87.0	3
149–150	48.0	54.0	11
143–144	51.0	51.0	32
127–128	42.0	42.0	3
125–126	42.0	47.0	3
14–15	28.2	24.6	10

This method was adopted as larger specimens were obtained with less difficulty, and was used only after we had satisfied ourselves that no constant differences were noted in the "fore" and "after" milk, as can be seen from Table 2. The specimens used in this table were obtained from women who had large amounts of milk.

SOURCE OF MATERIAL

The specimens of milk were obtained from various sources, namely, from the Outpatient Department of the Massachusetts General Hospital, the Boston Lying-In Hospital, the Clinics of the Boston Baby Hygiene Association, the Boston Wet Nurse Directory, and from private patients.

In Table 3 we have arranged, according to the period of lactation, the results obtained on all the 327 samples of milk examined. In many instances, the results represent averages of as many as ten specimens collected from one woman. Figure 1 shows a curve of the average concentration of chlorin and the maximum variation for each week as based on the results in Table 3.

TABLE 3.—AVERAGE OF RESULTS ON DETERMINATION OF CHLORIN IN 327 SPECIMENS OF HUMAN MILK TAKEN FROM THE FIRST TO THE SEVENTY-FOURTH WEEK OF LACTATION

Mg. Chlorin per 100 C.c. of Milk

1st Wk.	2d Wk.	3d Wk.	4th Wk.	5th Wk.	6th Wk.	7th Wk.	8th Wk.	9th Wk.	10th Wk.	11th Wk.	12th Wk.	13th Wk.	15th Wk.	16th Wk.	17th Wk.	18th Wk.
120.0	30.0	49.0	73.5	21.9	64.5	54.3	36.2	44.7	50.0	31.0	48.0	96.0	112.0	71.0	60.0	75.0
81.5	28.0	39.7	86.0	49.0		71.9		49.2	26.9	43.3		73.8	45.7	105.0	111.0	40.8
36.0	41.0	36.0	69.0	39.0		36.0		60.8	52.0	51.0		60.0	43.8		47.0	
81.0	114.0	37.2	30.0	43.5		39.0		38.0		61.5		42.0			28.3	
61.0	117.0	97.0	72.8	31.0		45.0									33.0	
111.0	111.0	94.0	77.7												34.0	
51.0	111.0	44.5	82.0													
46.5	99.0	42.0	36.0													
58.5	60.0	42.0														
61.0	87.0	81.0														
40.5	38.9	52.0														
72.7	75.0	55.1														
101.8	49.8	40.6														
75.0	58.6															
111.4	102.3															
42.0	65.0															
158.3	56.0															
78.0	50.6															
	60.0															

20th Wk.	21st Wk.	22d Wk.	23d Wk.	24th Wk.	26th Wk.	28th Wk.	29th Wk.	34th Wk.	39th Wk.	43d Wk.	47th Wk.	48th Wk.	51st Wk.	52d Wk.	74th Wk.
38.2	30.0	43.5	72.5	43.8	19.5	38.4	53.6	82.8	36.6	23.4	67.0	49.2	31.0	60.0	34.8
47.3	66.0	106.0	24.0		52.2		56.7	73.8						18.0	
45.4	40.2	24.9												35.6	
54.0	42.0	41.1													
		101.3													

The results presented in Table 3 show that our average after the first two weeks of lactation is 52.6 mg. chlorin per 100 c.c. of milk. The average, if all periods of lactation are considered, is 58.2. This approaches the average results to be found in the literature as completed by Holt, Courtney and Fales.[6] As has been noted formerly, there is a tendency toward slightly high concentration of chlorin to occur during the first week, as shown in the accompanying illustration, after which the average remains about constant up to the seventeenth month.

Extreme variations were noted in the chlorin content of specimens from women in the same period of lactation and in specimens collected from individuals during a single day. Table 3 and the second curve in the illustration are based on averages, and show, in a measure, only the

6. Holt, L. E.; Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. **10**: 229 (Oct.) 1915.

frequency and the degree of these variations. In some instances, there was more than 300 per cent. difference in the chlorin content in individual specimens taken from one woman during twenty-four hours, more than 1,000 per cent. in specimens from different women at the same period of lactation. Figures as low as 14.1 mg. and as high as 156.8 have been obtained. This extreme variation may be accounted for by the fact that the specimen of milk was obtained from a woman who had had extreme symptoms of one of the toxemias of pregnancy and also because of her small daily output of milk. Variations nearly as great, however, may occur between specimens from normal women in the same period of lactation. In searching for a possible cause for these extreme variations of chlorin content in human milk, the data have been studied from different points of view. The influence of the
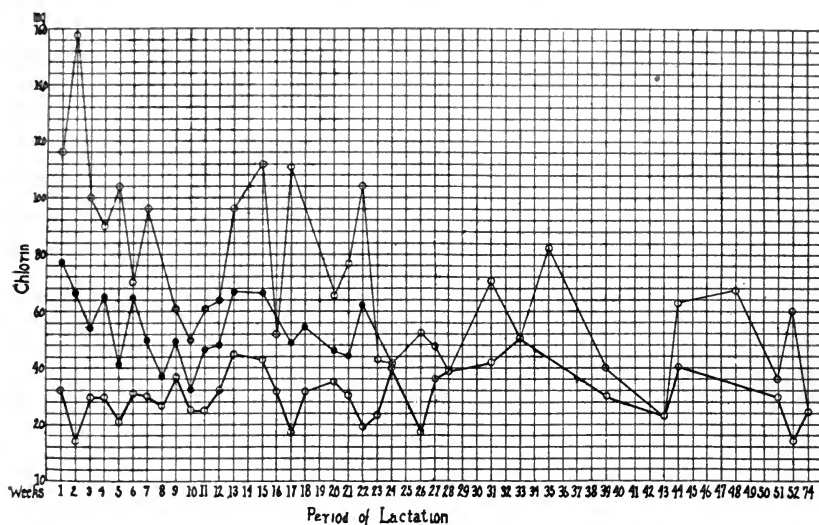
Curves of maximum (upper curve), average (middle curve) and minimum (lower curve) amounts of chlorin in human milk.

period of lactation, of the volume of the secretion, of the time of collection during the day, of the ingestion of food and of psychic stimuli have been considered. As a basis for comparing the possible effects of these factors, it was thought advisable to establish, first, a normal figure. For this purpose, we have collected the results obtained on the milk of women whose environment, diet and temperament were most accurately known. These data were obtained largely from private patients living under most favorable circumstances and who were considered to be normal, physically and psychically, and who were giving an adequate amount of milk of such a quality that their babies developed normally for a period of at least six months.

The results obtained on the milk of these selected subjects are presented in Table 4.

TABLE 4.—CHLORIN CONTENT OF SPECIMENS FROM NORMAL SUBJECTS
(LACTATING TYPES)

Name	Number	Mg. Chlorin per 100 C.c. of Milk			Period of Lactation, Weeks	Approximate Amount of Milk in 24 Hours, C.c.
		Before Nursing	After Nursing	Middle Nursing		
Mrs. W.	2	47.4	....	....	11	750
Mrs. W.	3	....	39.3	....	..	750
Mrs. T.	25	25.9				
Mrs. T.	26	....	34.2	....	2	750
Mrs. H.	13	....	....	36.0	3	600
Mrs. H.	88	....	....	32.0	10	750
Mrs. S.	16	37.2	....	....	3	660
Mrs. St.	45	59.0	....	....	7	720
Mrs. St.	46	....	50.0			
Mrs. St.	149	48.0	....	....	11	450
Mrs. St.	150	....	54.0	....	11	
Mrs. R.	92	....	....	43.0	5	750
Mrs. Ra.	93	....	....	44.0	5	750
Mrs. F.	108	....	49.4	....	20	900
Mrs. F.	109	....	45.3	....	20	900
Mrs. F.	132	....	....	47.0	20	900
Mrs. F.	133	47.0	....	....	20	900
Mrs. F.	134	42.0	....	....	20	900
Mrs. F.	135	47.0	....	....	20	900
Mrs. F.	136	47.0	....	....	20	900
Mrs. F.	138	42.0	....	....	20	900
Mrs. F.	139	36.0	....	....	20	900
Mrs. F.	140	37.0	....	....	20	900
Mrs. F.	141	35.0	....	....	20	900
Mrs. F.	143	51.0	....	....	30	750
Mrs. F.	144	....	51.0	....	30	750
Mrs. I.	312	29.4	....	....	52	1,200
Mrs. I.	313	....	30.0	....	52	1,200
Mrs. Str.	298	....	....	30.0	5	750
Mrs. Str.	299	....	....	31.0	5	750
Mrs. Str.	300	....	....	32.0	5	750
Mrs. Str.	301	....	....	32.0	5	750
Mrs. Str.	302	....	....	32.0	5	750
Mrs. Str	303	....	....	30.0	5	750
Mrs. Str.	304	....	....	30.0	5	750
Mrs. Wi.	294	....	....	30.0	24	750
Mrs. K.	251	40.2	....	....	22	750
Mrs. B.	201	38.4	....	....	28	750
Mrs. Kv.	166	40.8	....	....	17	840
Mrs. Q.	125	42.0	....	....	3	750
Mrs. Q.	126	47.0	....	....	3	750
Mrs. D.	101	30.0	....	....	4	750
Mrs. Sp.	14	24.6	....	....	10	600
Mrs. Sp.	15	....	28.2	....	10	600
Mrs. G.	316	40.8	....	....	9	630
Mrs. G.	317	....	36.0	....	9	630
Mrs. G.	318	37.0	....	....	9	630
Mrs. G.	319	....	35.0	....	9	630
Mrs. G.	320	37.8	....	....	9	630
Mrs. G.	321	....	37.8	....	9	630
Mrs. G.	322	41.4	....	....	9	630
Mrs. G.	323	....	38.4	....	9	630
Mrs. Sti.	324	....	....	30.0	39	1,100
Mrs. Sti.	325	....	....	32.5		
Mrs. Sti.	326	....	....	34.0		
Mrs. Sti.	327	....	....	40.0		

From the results presented in Table 4, it will be seen that the chlorin content of milk from so-called strictly normal subjects has a relatively narrow range of variation, after the first week of lactation, namely, from 30 to 50 mg. per 100 c.c. of milk (average 38.1 mg.). Attention should also be called to the fact that in these subjects little variation is noted in specimens taken before and after nursing and at

various periods during the day. The effect of the period of lactation on the amount of chlorin in human milk can be seen from the determinations recorded in Tables 3 and 4. Table 3, in which specimens from all types of patients are considered, shows that during the first two weeks of lactation there is a definite tendency for the chlorin content to be high, and that after this period no constant change takes place. Specimens with high and with low chlorin content will be found to occur at all stages of lactation. Table 4, on the other hand, shows that in "normal" subjects such variations do not occur during the first six

TABLE 5.— CHLORIN CONCENTRATION OF SPECIMENS OF HUMAN MILK FROM NORMAL WOMEN COLLECTED AT INTERVALS DURING THE DAY

Number	Name	Time	Amount Collected, Oz.	Daily Amount, Oz.	Mg. Chlorin	Period of Lactation, Weeks
210	Mrs. L.	6 a.m.	...	25¾	43.7	21
211	Mrs. L.	9 a.m.	...	....	37.5	21
212	Mrs. L.	12 m.	...	....	36.0	21
213	Mrs. L.	3 p.m.	...	....	39.0	21
214	Mrs. L.	6 p.m.	...	....	45.0	21
215	Mrs. L.	9 p.m.	...	....	41.4	21
192	Mrs. F.	8 a.m.	6¾	....	15.0	26
193	Mrs. F.	8 p.m.	6½	34½	19.5	26
186	Mrs. A.	6 a.m.	3½	....	32.0	17
187	Mrs. A.	9 a.m.	4¾	....	40.8	17
188	Mrs. A.	12 m.	2	....	32.0	17
189	Mrs. A.	3 p.m.	2¾	....	31.8	17
190	Mrs. A.	6 p.m.	3	....	31.8	17
191	Mrs. A.	3 p.m.	2½	....	32.0	17
170	Mrs. W.	6 a.m.	5¾	35	28.8	22
171	Mrs. W.	9 a.m.	8	....	27.0	22
172	Mrs. W.	12 n.	4¾	....	24.0	22
173	Mrs. W.	3 p.m.	...	....	26.8	22
174	Mrs. W.	6 p.m.	5	....	22.8	22
175	Mrs. W.	9 p.m.	...	....	26.8	22
176	Mrs. T.	3 p.m.	...	...	32.3	22
177	Mrs. T.	12 n.	...	....	26.3	22
134	Mrs. F.	12 n.	...	....	44.5	22
136	Mrs. F.	3 p.m.	...	....	47.0	22
64	Mrs. Q.	12 m.	...	25	108.0	1
65	Mrs. Q.	3 p.m.	...	....	108.0	1
66	Mrs. Q.	6 p.m.	...	....	108.0	1
67	Mrs. Q.	10 p.m.	...	....	108.0	1
68	Mrs. Q.	2 a.m.	...	....	112.0	1
69	Mrs. Q.	6 a.m.	...	....	117.0	1
70	Mrs. Q.	9 a.m.	...	....	112.0	1
316	Mrs. G.	3 p.m.	...	....	38.4	12
318	Mrs. G.	5 p.m.	...	....	36.0	12
320	Mrs. G.	10 p.m.	...	....	37.8	12
322	Mrs. Q.	6 a.m.	...	....	39.9	12

months of lactation. From these observations we feel justified in concluding that after the first two weeks of milk secretion the concentration of chlorin in human milk is not related to the period of lactation. The effect of the volume of the milk and of the time of collection during the day on the concentration of the chlorids is shown in Table 5. The subjects represented in this table were wet nurses at the Boston Wet Nurse Directory, who were normal mothers giving relatively large amounts of milk. It will be noted that the average figure, as in the table of "normal" subjects, is about 40 mg., and that the chlorin concentration of the milk varies little in the specimens collected at three-

hour intervals during the day and bears no constant relation to the volume of milk obtained at three hour periods. There is, however, a tendency for somewhat higher figures to occur in the early morning and late evening specimens.

In Table 6 we have collected all the specimens of milk with the chlorin concentration above 50 mg. per 100 c.c. Although the subjects from whom these specimens were secured, were not known to us personally in all instances, they were mothers who were giving an amount of milk inadequate for the growth of the infant. From Tables 5 and 6 it will thus be seen, that after the supply of milk has been established, normal mothers, giving relatively large amounts of milk, always have between 30 and 50 mg. chlorin per 100 c.c. of milk, that this concentration does not vary constantly with the amount of milk obtained at three hour periods and that high chlorin concentrations tend to occur among mothers who for some reason cannot be regarded as "lactating types."

TABLE 6.—CHLORIN CONTENT OF SPECIMENS OF NORMAL SUBJECTS OF NONLACTATING TYPE

Number	Name	Mg. Chlorin per 100 C.c.	Period of Lactation, Weeks	Daily Approximate Amount of Milk, C.c.
295	Mrs. S.	82.0	4	210
308	Mrs. S.	69.0	6	180
309	Mrs. S.	60.0	6	180
289	Mrs. P.	114.0	22	300
290	Mrs. P.	102.0	22	300
291	Mrs. P.	98.0	22	300
257	Mrs. S.	90.6	5	200
258	Mrs. S.	114.0	5	200
227	Mrs. W.	67.0	48	15 oz. 450
168	Mrs. H.	75.0	3	15 oz. 450
169	Mrs. H.	87.0	3	15 oz. 400
197	Mrs. H.	77.7	5	12 oz. 360
117	Mrs. S.	96.0	13	10 oz. 350
59	Mrs. P.	112.0	15	250
248	Mrs. P.	51.6	24	120
249	Mrs. P.	52.8	24	120
54	Mrs. P.	86.0	4	15 oz. 400
89	Mrs. W.	59.0	4	10 oz. 300

The results presented in Table 5 indicate also that the chlorin content of milk is not influenced by the food as the values of milk chlorids in the first morning nursing, when no food had been taken since the evening of the previous day, were essentially the same as those obtained in the late afternoon and early evening, a time when one would expect the effects of ingested food to be apparent. It is, of course, conceivable that the chlorid content of milk might be altered by feeding diets poor or rich in sodium chlorid for relatively long periods, or by the administration of relatively large amounts of the same for short periods. For lack of suitable experimental material, it was impossible, unfortunately, to extend this line of inquiry in connection with our studies of human

milk. We have, however, carried out a considerable number of experiments dealing with this subject on goats and cows, the results of which work will be published at an early date.

TABLE 7.—CHLORIN CONTENT OF MILK FROM "UNSTABLE" SUBJECTS

Number	Name	Mg. Chlorin per 100 C.c. of Milk			Approximate Daily Amount of Milk, C.c.	Period of Lactation, Weeks
		Middle Nursing	Before Nursing	After Nursing		
8	Mrs. R.	....	25.0	....	600	11
9	Mrs. R.	....	....	37.1	600	11
10	Mrs. R.	....	32.0	....	600	11
11	Mrs. R.	....	....	64.0	600	11
102	Mrs. H.	....	....	40.6	350	1
103	Mrs. H.	....	76.5	....	350	1
180	Mrs. B.	30.0				
184	Mrs. B.	...	63.0	....	600	3
185	Mrs. B.	....	....	60.0		
198	Mrs. S.	....	45.0	....	600	13
199	Mrs. S.	....	....	102.7	...	13
240	Mrs. S.	72.0	....	....	...	17
241	Mrs. S.	66.0	....	....	...	17
216	Mrs. N.	....	40.0	....	600	3
219	Mrs. N.	78.0	....	....	600	3
47	Mrs. D.	....	90.0	....	250	4
48	Mrs. D.	....	57.0	....	250	4
309	Mrs. S.	....	41.4	....	700	5
310	Mrs. S.	....	....	31.2	700	5
296	Mrs. M.	....	48.0	....	...	2
297	Mrs. M.	....	....	72.0	...	2
268	Mrs. K.	50.0	....	....	...	2
269	Mrs. C.	50.0	....	....	...	2
		55.0	....	....	700	2
272	Mrs. C.	84.0	....	....	700	2
273	Mrs. C.	47.0	....	....	700	5
275	Mrs. C.	49.0	....	....	700	2
282	Mrs. G.	49.0	....	...	700	5
283	Mrs. G.	49.0	....	....	...	5
284	Mrs. G.	54.0	....	....	...	5
285	Mrs. G.	59.0	....	....	...	5
286	Mrs. G.	42.0	....	....	...	5
264	Mrs. I.	36.0	....	....	...	5
265	Mrs. I.	43.8	....	....	...	3
266	Mrs. I.	49.8	....	....	...	3
267	Mrs. I.	33.0	....	....	...	3
221	Mrs. N.	72.0	....	....	600	3
205	Mrs. N.	49.8	....	....	600	2
216	Mrs. N.	40.0	....	....	600	3
217	Mrs. N.	43.8	....	....	600	3
218	Mrs. N.	42.0	....	....	600	3
219	Mrs. N.	78.0	....	....	600	3

In view of the well recognized effect of psychic stimuli on the composition of the urine and of the saliva, it seemed possible that this factor might be a cause for the variation in the concentration of chlorin in human milk. It was noted that in most instances the variations were found in specimens from women whose babies were growing unsatisfactorily, and who for this or other reasons may be classified as irritable or emotional mental types. In some instances, the daily volume of milk was sufficient for the baby but was subject to considerable variation. In Table 7 we have arranged the results of the analyses of specimens of milk from these so-called "unstable" types. It will be seen that in the milk of such mothers variations of as much as 100 per cent. occur in the chlorin content of specimens of milk obtained at different periods.

SUMMARY

A study of the chlorin content of 327 specimens of human milk has been made by the use of the McLean-Van Slyke titration method. It has been shown from these determinations that the average chlorin content of human milk from all types of mothers and at various stages of lactation is 38.1 mg. per 100 c.c. of milk. It has been noted that during the first two weeks of lactation, the chlorin content of human milk is somewhat higher. Specimens containing high and low chlorin concentration may be found in all stages of lactation. It has been found that the milk of strictly normal women giving a normal amount of milk has a relatively narrow range of variation in the chlorin concentration of their milk.

Observations on the relation of ingestion of food, of the time of collection of the specimens, of the volume of secretion and the effect of psychic stimuli, to the variation in the chlorin concentration of human milk have been made. It was found that in normal subjects the food intake and the time of day that the collection is made cause no outspoken change in the chlorin content of the milk. There is a slight tendency toward somewhat higher concentrations in specimens collected in the early morning and late evening. In women whose daily output is very large, there is an unmistakable tendency to the production of milk of a low chlorin content, and conversely those with a small amount of milk more frequently secrete milk containing a relatively high concentration of chlorids. This fact probably accounts for the statements in the literature to the effect that the concentration of the mineral constituents of the milk increase with each month of lactation, a finding which would, of course, go hand in hand with the decreased daily volumes usually noted in the later stages of milk production.

Our results would seem to indicate that the chlorin content of the milk can be affected markedly by psychic stimuli, as in phlegmatic mothers living under good conditions the chlorin content of the secretion remains constant from day to day and hour to hour. In the case of mentally unstable types, women also living under favorable conditions, large variations, frequently amounting to as much as 100 per cent., may occur. It has been noted that the babies with mothers of this type very frequently show evidences of intestinal indigestion and that as a rule the mothers are able to nurse their babies for relatively short periods.

CONCLUSIONS

1. The "salt" content of human milk is subject to great variations during all periods of lactation.

2. Estimation of the chlorin content of human milk can be obtained only by examining specimens from all nursings during the day.

3. The average chlorin concentration of milk from all types of women at all periods of lactation is 58.2 mg. per 100 c.c. of milk; the average after the second week of lactation is 52.6 mg.

4. "Normal" mothers, giving large amounts of milk, show a minimum variation in the chlorin concentration of their milk, with an average of 38.1 mg.

5. The greatest variation in the chlorin content of milk is found in specimens from "nervous" women.

6. Diet is not a cause for the variation in the chlorin concentration of human milk.

7. The chlorin concentration of milk from women, after the second week of lactation, who give large amounts of milk tends to be low and conversely the milk from women giving small amounts of milk is high in chlorin.

INFANTILE SCURVY FOLLOWING THE USE OF RAW CERTIFIED MILK *

HAROLD K. FABER, M.D.
SAN FRANCISCO

From the fact that most textbooks on diseases of children state that scurvy may occur on a diet of raw milk, the extreme rarity of the occurrence is, perhaps, not sufficiently appreciated. The only direct references to such cases that I have been able to find are in the classic report of the American Pediatric Society [1] and in a paper by Dr. J. L. Morse.[2] The first of these authorities, under the heading "Food used at or shortly before scurvy developed," states: "Raw milk alone, 4; with breast milk and amylaceae, 1; total 5." No further details of the cases are furnished. The total number of cases in this report in which the character of the food is specified, is 356. Morse's report, embracing fifty-eight cases, includes one case on raw milk, but the length of time it had been administered and other details are not given. It is a curious fact that many more cases of scurvy are reported in infants fed on breast milk than on cow's milk feeding; in the American Pediatric Society report there are ten, and in Morse's report, three breast milk cases.

The case reported herewith is apparently the first in which raw milk had been given practically from birth, and it has the additional value in more clearly defining the issue, that certified milk exclusively was employed.

REPORT OF CASE

History.—A girl, aged 10 months, was admitted to the Children's Clinic of Leland Stanford Junior University Medical School, Oct. 28, 1919. Complaint: "rheumatism." Father and mother are healthy, young American born people of Italian parentage, with no history or indicaton of syphilis or other disease. The patient is the first-born. There have been no previous pregnancies.

The baby was born at full term weighing 6 pounds, 7 ounces. She was never breast fed but from the first has been given on physician's advice a formula consisting of raw certified milk, Mead's dextrimaltose No. 1 and boiled water, with the addition to each bottle of the following preparation: Sodium citrate, 3 drams; distilled water, 2 ounces. Ten drops have been added to each feeding.

The formula was at first made up of one part of milk and two parts of water; at about 2 months it was changed to a half-and-half mixture, and at 9 months, to a two-thirds mixture. A teaspoonful of dextrimaltose was added to each bottle. Seven bottles a day, at three hour intervals, were given until the baby was 9 months old, since then three bottles a day have been given.

The mother states that she has always offered the baby 8 ounces of the milk mixture and allowed her to take as much of it as she would. Until the present illness began the baby made, apparently, satisfactory progress in weight and growth. Shortly after the symptoms began, the diet was changed so that the infant received three bottles a day supplemented by farina, eggs, Italian pastes with a little olive oil, but no fresh vegetables, fruit or fruit juices have ever been given. Except for two days, when the baby was 6 months old, nothing but certified milk has been used. The mother was very emphatic on this point and brought a bottle of the milk to corroborate—as it did—her assertion. The formula has never been boiled or heated, except when it was warmed at feeding time. From the feeding history it would appear that the physician in giving the mother his instructions had kept in mind the dangers of scurvy from heated milk.

Present Illness. — The first symptoms were noticed by the mother about July 1, when the baby was 6 months old. In putting on the baby's stockings, the mother noticed that the left tibia was tender, and about a month later the baby cried when the shoes were put on. The tenderness increased slowly. About a month ago (toward the end of September) swelling and pain in the knees were noticed, and a week later the mother found one morning that the mouth was bloody. On investigation she saw that the blood was coming from the gums.

Questioned as to trauma, the mother stated that in August, when the child was lifted from a chair the left foot caught in one of the rungs and the baby cried for a moment. In September, the baby had "fever" for three days, and since then has seemed to be "sore all over," but suffers most when the napkins are changed or stockings are put on. A diagnosis of "rheumatism" was made by the physician, but the mother was not satisfied with this diagnosis.

Physical Examination.—The baby is pale and pasty looking and very irritable when handled. The face is full, but the body is not well padded. The legs are flexed with the thighs everted and are held motionless. There is no craniotabes nor bossing. There is slight seborrhea of the scalp. Seven teeth are fully erupted. The gums around all these, but especially around the upper incisors, are swollen, purplish in color and bleed readily when touched. There is slight beading of the ribs, and a shallow Harrison's groove. The abdomen is not protuberant. Heart and lungs are normal. The liver is palpable about 2 cm. below the costal margin. The spleen is not palpable. The genitalia are somewhat inflamed. On the buttocks are a number of small nearly healed excoriations. The lymph nodes are not enlarged. The wrist epiphyses are moderately enlarged but not tender. The lower femoral epiphyses are much enlarged, and the soft tissues over them are thickened. The knees are acutely tender, and motion is evidently very painful. The ankles and lower tibiae are also somewhat swollen and tender to pressure. About the right malleolus there is a faint bluish discoloration suggestive of a deep ecchymosis.

Impression: Scurvy and slight rickets.

Laboratory Examination.—Nov. 3, 1919: Erythrocytes, 4,219,000; hemoglobin 75 per cent.; leukocytes, 12,300; polymorphonuclears, 55 per cent.; lymphocytes, 40 per cent.; large mononuclears, 3 per cent.; transitionals, 2 per cent. The red blood cells were normal in shape, size and coloring. No normoblasts, megaloblasts or malarial parasites were seen.

November 4: Wassermann negative.

Roentgen-Ray Examinations.—Oct. 31, 1919: "Examination shows thickening along the diaphysis sides of the epiphyseal lines of all the long bones of the legs and forearms; slight periostitis about the upper part of the right tibia; apparently slight posterior displacement of the epiphyses of both femora."

November 4: "Further examination of both knees shows evidence of posterior displacement of the epiphyses of both femora; thickening along the diaphysis side of the epiphyseal line, as previously reported."

November 15: "Examination of both legs, for comparison, shows evidence of thickening along the diaphysis side of the epiphyseal lines of all the long bones; considerable periostitis along the shafts of the long bones."

November 25: "Examination of both legs, for comparison, shows decrease in the thickening about the epiphyseal lines; periostitis about the same as at last examination."

Treatment.—The child was put on a top milk mixture with additions to the diet of cooked cereals, vegetable purees, yolk of egg, baked potato and 4 ounces of orange juice daily. No medication was given.

Later Progress.—The improvement was so rapid that the child was discharged in nine days (November 6) from the hospital with instructions to the mother to bring the child to the clinic. In spite of the posterior displacement of the lower epiphyses of both femurs, the baby was moving both legs voluntarily by November 4. The general appearance was greatly improved. The gums had resumed their normal color. The legs were still considerably enlarged at knee and ankle but were only slightly tender. Orange juice, 2 ounces a day, was continued. The child when last seen in the clinic, December 6, was practically normal in appearance and had gained about a pound and a half in the month since her discharge from the hospital.

COMMENT

Clinically, this case was typical scurvy. The diagnosis was fully corroborated by roentgenogram and by the prompt and complete disappearance of symptoms without medication on a diet rich in antiscorbutic substances. Mild rickets was also undoubtedly present.

The principal interest of this case lies in the clear and complete dietary history extending from birth to the time of the patient's discharge from the clinic. The parents were intelligent and apparently sure of their facts. That raw certified milk had been used continuously seems to be beyond question. The undoubted extreme rarity of scurvy in infants fed on raw cow's milk demands a discussion of the possible causes of scurvy in this infant.

Two explanations may be advanced, first, that the amount of milk taken was too small; second, that the antiscorbutic vitamin was partly or wholly destroyed by some other agent than heat.

The experimental work of Chick, Hume and Skelton [3] explained certain discrepancies in the conclusions of previous investigations on the antiscorbutic vitamin content of raw cow's milk by showing that while this vitamin is present in cow's milk, its concentration is low. Guinea-pigs receiving less than 50 c.c. of cow's milk a day invariably developed scurvy. This observation has been confirmed by several workers. In a recent investigation [4] I found a somewhat higher concentration in raw milk produced near San Francisco but noted the invariable appearance of scurvy when less than 30 c.c. was fed. The

3. Chick, H.; Hume, E. M., and Skelton, R. F.: The Antiscorbutic Value of Cow's Milk, Biochem. J. **12**:131, 1918.

4. Faber, H. K.: Sodium Citrate and Scurvy, Proc. Soc. Exper. Biol. & Med. **17**:140, 1920.

experimental evidence, therefore, goes to show that the occurrence of scurvy in man might be due to too low an intake of raw milk, as well as to the use of milk in which the vitamin had been destroyed by heat or by other agents.

In the present case, a dilute formula (1 part milk, 2 parts water) was used up to the age of 2 months, and thereafter the strength was only 1 part milk and 1 part water. The exact quantities taken daily are not known, but the mother stated that the baby, except when very young, usually finished a bottle of 8 ounces every three hours, a total of seven bottles daily. It appears likely, therefore, that between the ages of 2 and 9 months, the period during which scurvy developed, the baby must have taken an average of nearly 28 ounces of milk daily. Since an intake of this amount is not often exceeded by infants between the ages stated, and since scurvy so rarely occurs during feeding with raw milk, it seems unlikely, though perhaps not impossible, that a quantitative deficiency could have been responsible for the occurrence of scurvy in the present case.

The second possibility—that the antiscorbutic vitamin had been destroyed—remains to be considered. Aging of the milk can hardly be thought of, since the vigilant milk commission of the San Francisco County Medical Society demands prompt marketing of all milk which it certifies. The possibility that the sodium citrate, added to each bottle taken by the patient since the first week of life, may have had a deleterious effect on the antiscorbutic vitamin deserves consideration.

Alkalization has been proposed by Hess and Unger [5] as one of the causes of destruction of vitamin. They state that even such small quantities of alkali as are contained in certain infant foods may be sufficient to destroy the antiscorbutic vitamin in milk.[6]

A determination of the effect of sodium citrate on the hydrogen-ion concentration of a sample of raw milk, done through the kindness of Dr. E. C. Dickson, showed that an addition to the amount of 0.25 per cent. lowered the P_H from 6.45 to 6.50; of 0.5 per cent., to 6.95; and of 1 per cent., to 7.05. The addition of 10 drops of an 18 per cent. solution of sodium citrate to 8 ounces of whole milk—the approximate amounts in the present case—giving a strength of 0.05 per cent., would lower the acidity by considerably less than P_H 0.05; probably, as shown by the plotted curve, by less than P_H 0.01. Such an alteration of acidity should be regarded as probably insignificant.

---

5. Hess, A. F., and Unger, L. J.: The Deleterious Effect of the Alkalization of Infant's Food, J. A. M. A. **73**:1353 (Nov. 1) 1919.

6. It is only fair to state that this assertion has been disputed by several competent clinicians. (See discussion following Hess and Unger's report.) Mead's dextri-maltose No. 1 is stated by the manufacturers to contain 2 per cent. added sodium chlorid, but it apparently contains no added alkali.

In a series of experiments [4] it was shown that additions of from 0.25 to 2 per cent. of sodium citrate to raw milk apparently reduced the antiscorbutic vitamin content, since in eight out of nine guinea-pigs fed on citrated milk, scurvy developed, while in the control series of eight animals, fed on raw milk alone, scurvy developed in only two, both of which took an average of less than 34 c.c. of milk daily. None of the animals in the citrate series took less than 35 c.c. daily and the average of the citrate series was 41.8 c.c. as compared with an average of 40.7 c.c. for the controls. It should, however, be pointed out that none of the experimental animals received as little sodium citrate as was given to the human case here reported. In the latter the concentration of sodium citrate in the formula was approximately 0.05 per cent., or a total of about 0.84 gm. daily. The long period of continuous administration may, however, be considered. Knowing that the concentration of vitamins in cow's milk is low, that the concentration was reduced to one third for the first two months and to one half during the next seven months, may not the amount of added citrate have been sufficient to lower the vitamin concentration just below the scorbutic threshold?

Assuming this to have been the case, I do not feel that we have as yet sufficient evidence to attempt an analysis of the modus operandi of sodium citrate in injuring the antiscorbutic vitamin. The degree of alkalization it produced in the patient's food was probably negligible. Bosworth and Van Slyke's [7] observation that sodium citrate forms in milk a soluble sodium paracaseinate would not appear relevant to the question of scurvy. Certainly, the citrate ion—present in large amounts in so many antiscorbutic foods—cannot be brought into discussion. Finally, in spite of the presence of a certain amount of positive evidence and in the absence of other apparent antiscorbutic factors, it is not certain that in the present case sodium citrate was actually at fault. It would, however, appear justifiable to regard sodium citrate in formula preparation with considerable distrust and to give preference to other substances, such as barley water, over the mineral salts when we wish to alter the coagulability of cow's milk.

SUMMARY

1. An infant fed almost from birth on modified raw certified milk, to which small amounts of sodium citrate were added, developed scurvy at the age of 6 months.

2. It is possible, but not proved, that sodium citrate may have partly destroyed the antiscorbutic vitamin.

3. The use of sodium citrate in infant feeding over long periods should be provisionally regarded as dangerous.

7. Bosworth, A. W., and Van Slyke, L. L.: Why Sodium Citrate Prevents Curdling of Milk by Rennin, Am. J. Dis. Child. **7:**298 (March) 1914.

INDICANURIA IN THE NEW-BORN [*]

B. E. BONAR, M.D.

CHICAGO

This study was undertaken for the purpose of observing the reaction for indican in the urine of the new-born under physiologic conditions

Momidlowski [1] tested for indican in the urine of three healthy infants between the ages of 10 and 12 days. He obtained intense reactions which on the second and third day following were negative or showed only traces.

Von Reuss [2] found indican in the urine in breast fed children during the first nine days of life rather frequently, often without the observation of any clinical symptoms. He states that it occurs in the well nourished, in the undernourished, in the constipated, and in diarrheic infants alike. Indican was not obtained on the first day and rarely on the second. It was most frequently found on the third and fourth days, but was found during the days following. As possible causes of this indicanuria, the absorption of indol from the intestinal content must be considered and also the parenteral formation of indican, which may be taken as a sign of tissue destruction. Von Ruess brings out the disproportion between the intensity of the indicanuria and the putrefactive manifestations in the stool. The fact that Hecht was unable to recognize indol in the meconium suggests that indican may result from the breaking down of tissue protein.

Maccone,[3] in a large series, records only one case in which the urine of the new-born was examined for indican and in this instance it was absent.

Technic.—The cases taken for study were from the nursery ward of the hospital. The urine of all infants delivered was examined. No cases were picked. The infants all were normal newly-born infants. The urines were examined during two different periods one month apart. No change in the routine care of the infants was made, except that daily specimens were collected by means of test tubes or Spicer's urinals. An unsuccessful attempt was made to examine single

---

1. Jahrb. f. Kinderheilk. **26**:199, 1893.

2. Ztschr. f. Kinderheilk. **111**:12, 1911.

3. Riv. di clin. Pediat. **27**:1, 1919.

specimens of morning urine from each infant every day for fifteen days. A complete urine examination was made whenever a positive indican reaction was found. All such examinations failed to reveal any pathologic findings. All urines were examined within a few hours after collection.

The tests were made with Obermayer's reagent, which was made up of strong hydrochloric acid of 1.19 specific gravity, to which had been added two parts to the thousand of ferric chlorid. The urine was precipitated with a weak solution of lead acetate and filtered through filter paper. Fifteen c.c. of the filtered urine were mixed with 15 c.c. of Obermayer's reagent, and 2 c.c. of chloroform were added. The tube was then slowly inverted several times to mix thoroughly and allowed to stand for five minutes before reading. No coloration or a very faint blue was considered a negative reaction (0). A definite but faint blue was regarded as a trace, ($\pm$); an undoubted blue was regarded as a one plus (+) reaction; a deep blue as a two plus (++) reaction, and a very deep blue as a three plus (+++) reaction. The results obtained are shown in the accompanying table.

Out of 338 specimens of urine tested, twenty-eight, or 8.2 per cent., showed positive indican reactions. In five cases a positive reaction was obtained more than once. The reactions occurred most frequently and were more intense on the third, fourth and fifth days. No reactions were obtained on the eighth, ninth, eleventh, twelfth and fifteenth days.

Of significance is the fact that indicanuria most frequently is obtained during that period of life when the transitory fever of the new-born, and the transition from meconium to milk stools occurs when the weight has reached the lowest point.

There are probably two sources from which indican is derived. The first is decomposition of tissue protein and the second is putrefaction of protein in the bowel. That destruction of tissue protein to a considerable extent occurs during the first few days of life and particularly during the first five or six days of life is no doubt true. There are several factors which seem to speak for this. An initial loss of weight is common during the first five days, a larger portion of which is due to loss of body fluids but evidently some destruction of tissue protein takes place during this period when the infant receives insufficient nourishment. The presence of a relatively high amount of uric acid in the urine of the new-born and the frequent finding of uric acid infarcts in the kidneys at autopsy brings forth further evidence of possible destruction of tissue protein. Nitrogen deficiency in the early days of life has been observed by some investigators. This finding would speak strongly for tissue destruction. However, such a deficiency has not been established with certainty as yet.

It has been found by Blumenthal[4] and Rosenfeld that a small quantity of indican is probably formed in the adult during fever. Scholz,[5] however, could not find an increase in indican due to breaking down of tissue protein.

TABULATION OF RESULTS

Case Number	Day															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	—	—	0	0	0	0	0	0	0	0	—	—	—	—	—	—
2	—	—	0	—	—	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	0	0	0	0	0	0	0	—	—	—	—	—	—
4	—	0	0	0	—	0	0	—	0	—	—	—	—	—	—	—
5	—	—	—	0	0	0	0	0	0	0	—	—	—	—	—	—
6	—	—	0	0	±	0	0	0	0	0	0	—	—	—	—	—
7	—	0	0	—	0	0	0	0	—	0	—	—	—	—	—	—
8	—	—	0	0	—	—	—	—	—	—	—	—	—	—	—	—
9	—	0	0	±	—	—	0	0	0	0	—	—	—	—	—	—
10	—	+++	±	+	0	0	0	0	—	0	—	—	—	—	—	—
11	—	—	0	++	±	±	—	0	0	0	—	—	—	—	—	—
12	—	0	0	0	0	0	0	0	0	—	—	—	—	—	—	—
13	—	—	0	0	0	0	0	0	0	0	0	—	—	—	—	—
14	—	—	—	+	—	—	0	0	0	0	0	—	—	—	—	—
15	—	—	+++	0	0	—	0	0	0	0	0	—	—	—	—	—
16	—	—	—	—	0	0	0	0	—	—	—	—	—	—	—	—
17	—	—	0	0	0	0	0	0	0	0	0	0	—	—	—	—
18	±	—	—	0	—	0	0	0	0	0	—	—	—	—	—	—
19	—	—	—	—	0	0	0	0	—	0	—	—	—	—	—	—
20	—	0	0	0	0	0	0	0	0	0	0	0	0	±	0	—
21	—	—	0	0	0	0	0	0	0	+	—	—	—	—	—	—
22	—	—	0	±	0	±	0	0	0	±	—	—	—	—	—	—
23	—	0	—	0	0	0	0	0	0	0	—	—	—	—	—	—
24	—	—	—	—	0	0	0	0	0	0	0	0	—	—	—	—
25	—	—	0	—	0	0	0	0	0	0	0	0	0	0	0	—
26	—	0	—	0	0	0	0	0	—	0	0	—	—	—	—	—
27	—	0	0	0	0	0	—	0	—	—	—	—	—	—	—	—
28	—	0	0	+	0	0	0	0	0	0	+	—	—	—	—	—
29	—	—	0	0	0	0	—	0	0	0	0	—	—	—	—	—
30	—	—	0	0	0	—	—	0	0	0	—	—	—	—	—	—
31	—	0	0	0	0	+	0	0	0	0	0	—	—	—	—	—
32	—	0	+	0	0	0	0	0	0	0	—	—	—	—	—	—
33	—	—	0	0	0	0	0	0	0	0	0	—	—	—	—	—
34	0	0	0	—	0	0	±	0	0	0	—	—	—	—	—	—
35	—	—	—	—	+	0	0	0	0	0	—	—	—	—	—	—
36	0	0	+++	+	—	0	0	0	0	—	—	—	—	—	—	—
37	—	—	0	0	0	—	—	—	0	0	0	—	—	—	—	—
38	—	—	—	—	—	—	—	—	0	0	0	—	—	—	—	—
39	—	—	0	0	0	0	—	—	0	—	—	—	—	—	—	—
40	—	—	—	—	—	—	—	0	0	—	—	—	—	—	—	—
41	—	—	0	0	0	0	0	—	0	—	—	—	—	—	—	—
42	—	—	0	0	0	—	0	0	0	0	0	0	—	—	—	—
43	—	—	—	—	0	0	0	—	0	0	—	—	—	—	—	—
44	0	0	0	0	0	0	0	0	—	0	—	—	—	—	—	—
45	—	—	—	0	0	0	0	0	—	0	0	0	—	—	—	—
46	0	0	—	+++	0	0	0	0	0	—	—	—	—	—	—	—
47	—	0	—	0	0	0	0	0	0	—	—	—	—	—	—	—
48	—	—	—	+++	0	—	—	—	—	—	—	—	—	—	—	—
49	—	0	—	—	+++	0	0	0	0	0	0	0	0	—	—	—
50	—	0	+	0	0	0	—	—	—	—	—	—	—	—	—	—
Total..	5	19	32	36	41	37	38	34	40	30	15	6	2	2	1	0
Positive...	1	1	5	8	5	3	1	0	0	2	1	0	0	1	0	0
Negative..	4	18	27	28	36	34	37	34	40	28	14	6	2	1	1	0

The total number of specimens examined was 338.

It was noticed in this series of cases that there was no apparent connection between the amount of weight lost and the frequency of a positive indican reaction. Likewise, no relationship between the transitory fever of the new-born and indicanuria could be established.

4. Charité Annalen, **27**:46, 1903.
5. Ztschr. f. phys. chemie **38**:513, 1903.

Although it is fairly evident that there is destruction of tissue protein during the early days of life it is hard to say whether some of the indican is formed by this method. The fact that a positive reaction was obtained on the first and second days would speak for a parenteral formation of indican. These results, however, cannot be considered as absolute proof of such a fact as it is impossible to rule out intestinal putrefactive processes at such an early date.

Decomposition of protein in the bowel is usually considered the chief source of indican in the urine. The finding of indicanuria in the new-born suggests two possibilities other than parenteral formation: increased absorptive action of the bowel, and increased putrefaction in the bowel. Von Ruess speaks of the disproportion between the putrefactive manifestations in the bowel and the intensity of the indican reaction. It is known that the bowel in its entire length contains bacteria within twenty-four hours after birth. The possibility of putrefaction of the intestinal contents is therefore apparent. The meconium at first is sterile, due probably to a lack of moisture. Introduction of fluids into the gastro-intestinal tract with consequent increase of gastric and intestinal juices might supply the moisture necessary to render the meconium an ideal medium for the growth of putrefactive bacteria and the formation of putrefactive substances. The transition of meconium to the milk stool is a gradual process taking several days. Thus it may be possible that during this transition to the milk stool of fermentative type of stool there is an increased amount of putrefaction in the bowel.

As regards an increased absorptive action of the bowel, the findings of Grulee and myself,[6] published in a recent paper, may have some bearing. It was found that during the first few days of life the intestines were frequently permeable to a foreign protein, egg-white, as shown by positive precipitin reactions in the urine. While these findings can only be interpreted as specific for the protein tested, it appears possible that in the intestine of the new-born there may be an increased absorption of not only egg-white but of other substances, such as indol.

SUMMARY

Indicanuria in the new-born occurred in twenty-eight, or 8.2 per cent., of 338 examinations, and in twenty cases of fifty examined.

Indicanuria, in all probability, may be considered physiologic, as it could not be associated with any pathologic findings clinically.

6. Am. J. Dis. Child., in press.

CLINICAL DEPARTMENT

POSTOPERATIVE RECURRENCE OF INTUS-SUSCEPTION *

MORRIS COHEN, B.S., M.D.

NEW YORK

To meet a case of intussusception in a patient who has been oper-ated on previously for the same condition has been considered an infre-quent occurrence. The following cases of postoperative recurrence of intussusception seen within a very short time at Lebanon Hospital, New York, have, because of the supposed rarity of the condition, prompted me to record them and to investigate the literature on the question.

REPORT OF CASES

I saw Cases 2 and 3 during both illnesses, Case 1 during the second illness, and Case 4 during the first attack.

CASE 1.—Arnold Z., aged 6 months, was brought to Lebanon Hospital, Aug. 23, 1917, having shown signs and symptoms of acute intussusception for the preceding six hours. A laparotomy was performed immediately by Dr. Book-man, who reduced a large ileocecal intussusception and the child made a rapid recovery. An appendectomy was performed at the same time. June 6, 1918, about ten months later, the child was seized with a second attack of intus-susception, was brought to Lebanon Hospital after four hours, when Dr. M. S. Kakels reduced an ileocecal intussusception. The child made an uneventful recovery and was discharged cured.

CASE 2.—Isidore G., aged 7½ months, was brought to Lebanon Hospital, March 17, 1919, almost in a state of extremis suffering from an acute intus-susception of less than twenty-four hours' duration. The child was operated on at once by the house surgeon. An ileocecal intussusception was completely reduced without any difficulty. During a period of about thirty hours the child did very well. It recovered from its shock, it had normal bowel move-ments, was very playful and to all intents and purposes was on the high road to complete recovery. However, after about thirty hours, the child again began to cry as if in severe pain, it again passed blood stained mucus, a mass could be felt in the abdomen and for a second time the child went into a condition of severe shock. The child was again operated on by Dr. M. S. Kakels who reduced another intussusception of the same type. A second attack so severe and within so short a period after the first was too great for the child to bear and it died soon after the operation.

The following case deserves lengthy description not alone because of the rarity of the condition, but also because of the atypical symptoms occurring during the second attack.

Case 3.—Evelyn J., 10 months old, was born of apparently healthy parents, had a normal birth and development, was breast fed up to 8 months and, was then placed on artificial feedings.[1] At the age of 6 months, the child was suddenly taken ill with an acute attack of intussusception of which the symptoms were unmistakable and well defined. The child was in shock, a well defined tumor could be felt in the abdomen and two diapers were stained with blood and mucus. Enemas were ineffectual. The child came to operation about four hours after the onset of symptoms, and Dr. L. M. Kahn reduced an ileocecal intussusception. The child made a very rapid recovery.

Nov. 6, 1919, about 3 a. m., four months after the first operation, the child was suddenly seized with repeated attacks of cramps at intervals of from ten to fifteen minutes. The attacks lasted up to about noon of the same day. An enema given that morning was returned with a very small amount of yellowish-brown fluid feces, some mucus but no blood. The last normal stool was passed in the morning of the preceding day. The child did not vomit.

I saw the patient for the first time at 3 p. m. The child looked perfectly well, was very playful, did not cry and its cheeks appeared to be of good color. The temperature per rectum was 100.4 F.; the pulse, 120. A complete physical examination was made and all findings were negative, except the abdominal signs. On gentle palpation the right side of the abdomen was found to be rigid and was apparently tender as the child would cry out and make attempts to push away the examiner's hand. The child did not react in the same way when the left side was manipulated. No masses could be felt in the abdomen or rectum and the finger withdrawn from the rectum showed no signs of blood or mucus. The signs at this time, indicative of an intra-abdominal surgical condition, were rigidity and tenderness, and, although the possibility of the presence of an intussusception suggested itself to me, I did not feel justified in making that diagnosis as I felt that I did not have sufficient evidence, especially after the child had been operated on previously for that condition. I left the patient with orders that nothing be given by mouth, that an enema be given with a rectal tube, and the returns noted for blood and mucus.

At 6 p. m. I was called again, and although the child's general condition was very good, she still showed the localized rigidity and tenderness on the right side of the abdomen. At this time also no masses could be felt in the abdomen; rectal examination was again negative, and there were no attacks of cramps during that afternoon. The temperature was normal, and the pulse was 124. One additional sign appeared at this examination and that was a very scant fecal movement with blood stained mucus following an enema.

My earlier suspicion that the child was suffering from a subacute attack of intussusception was now somewhat confirmed, but was made very doubtful by the absence of a palpable tumor in the abdomen or per rectum, by the absence of vomiting, and by the good general condition of the child. Another enema was given and the returns were again as last described.

The absence of diarrhea and rise in temperature made an ileocolitis very questionable. The rigidity and tenderness together with a history of cramps made it important to eliminate appendicitis, but the additional signs of blood stained mucus on two diapers, together with definite constipation, in spite of the important negative symptoms, suggested a recurrent intussusception so strongly that I felt a laparotomy was indicated.

The child was sent to Lebanon Hospital and Dr. Bookman reduced a very small ileocecal intussusception without any difficulty. An appendectomy was also performed. Up to the present, about ten months after the last attack, the child has been gaining weight and is in very good condition.

Dr. Henry Roth has brought to my attention another interesting case that I record with his kind permission.

---

1. Reported before Society of Alumni of Lebanon Hospital, Jan. 6, 1920.

CASE 4.—Gertrude L., aged 10½ months, was admitted to Dr. Henry Roth's private service, Jan. 30, 1919, suffering from an acute intussusception. Dr. Roth operated, and on opening the abdomen found that spontaneous reduction had already occurred, and at the site of the intussusception, which was confined to the ileum, there was a section of the bowel that was congested and edematous. The appendix was removed.

March 18, 1920, the child was again admitted to Lebanon Hospital suffering from another intussusception. At intervals, between the first and second attack, the patient had transient attacks of cramps and bloody stools. For a number of hours prior to admission, the child suffered from cramps, had vomited repeatedly and had passed blood stained mucus. A second operation, performed by Dr. Henry Roth, revealed an ileo-ileal intussusception involving the same portion of bowel as in the first instance. Reduction was not difficult, and the child was again discharged as cured.

Looking back over a series of forty-one cases of intussusception, treated at Lebanon Hospital during about eight years, the four cases mentioned above were the only ones in which postoperative recurrences were present, and these at intervals of ten months, thirty hours, four months and fourteen months, respectively. Fourteen of these forty-one patients died, and one patient left the hospital, the parents having refused to allow the child to remain for operation, thus leaving twenty-six patients discharged as cured. Of these, four had second attacks for which they were operated on again.

I have collected seventeen cases from the literature in which a total of thirty-six operations were performed for the reduction of intussusception. Added to the four cases reported in this paper we have a total of twenty-one patients who were operated on forty-four times. Two patients had three operations each. One patient who had had five attacks was operated on twice. The longest interval between operations was three years; the shortest thirty hours.

Kellock reports a most remarkable case of recurrent intussusception in a child who had five attacks with final recovery, operations having been performed to relieve the third and fifth attacks. Nonsurgical procedures, such as enemas and air inflation, reduced the others.

Mahon [3] reports one case of postoperative recurrence of intussusception three years after the first operation, and reviews six other cases that he had found in the literature. These six cases included two of Clubbe, occurring two and six months after the first operation, in a series of 144 cases; one case in a series of 100 cases reported by Adams and Cassidy; one case of Gould, in which two operations were performed on the same patient at an interval of one month; one case reported by C. N. Dowd, in which recurrence took place three and one-half months after first operation, and another case of Cleveland with recurrence after five weeks.

2. Lancet, **2**:154, 1912.
3. Guys Hosp. Gaz. **27**:356, 1913.

Turner [4] reports a case in which operation was performed three times, the third operation occurring nearly one year after the first attack. At the third laparotomy eighteen inches of ileum marked by tuberculous ulcers were resected, a lateral anastomosis was performed and the patient recovered. The same author records a case that showed unquestionable signs of intussusception three months after an operation for the same condition, but on entering the abdomen a second time, no intussusception was found. Spontaneous reduction probably occurred during anesthesia, as in the case of Dr. Roth. I have encountered one or two similar instances in which after an undoubted diagnosis of intussusception was made, laparotomy did not reveal the condition and in which, in all probability, spontaneous reduction had taken place during the administration of the anesthetic.

Eccles and Laidlaw,[4] in a series of 89 cases, report the case of one patient admitted on two separate occasions at an interval of three months. The patient recovered after two operations for ileocecal intussusception.

Allen,[6] in a review of twenty-seven cases of intussusception extending over a period of seventeen years, reports one case operated twice within four days at the Children's Hospital, Philadelphia.

Peskind [7] reports a case of intussusception in an infant, followed by obstruction of the bowels three weeks later and a second operation for intussusception.

Hipsley,[8] in a résumé of fifty-one cases of intussusception, mentions two cases of recurrence, one in which operation was done three times within a period of ten weeks, with final recovery, and a second case with recurrence after three months. He also refers to a case in the series, but of which he had no record, where recurrence took place four months after the first operation.

Graham [9] reports a case occurring in a boy, age 14 years, operated on for ileocecal intussusception May 30, 1916, and again July 11, 1916, when an irreducible intussusception was found. At the second operation four inches of the ileum were excised. Sections of the excised bowel showed the presence of small round celled sarcoma.

CONCLUSIONS

1. Repeated attacks of intussusception in individuals previously operated on for the same condition, although very unusual, are not as infrequent as we might have believed they were.

4. Lancet **1**:169, 1914.
5. St. Barth. Hosp. Rept. **47**:97, 1912.
6. Ann. Surg. **59**:258, 1914.
7. Am. J. Dis. Child. **14**:63 (July) 1917.
8. Med. J. Australia **2**:383 (Nov. 9) 1918.
9. Brit. M. J. **2**:801, 1916.

2. In the event of an acute abdominal condition in a child previously operated on for intussusception, we must not neglect to give serious consideration to a probable recurrence.

3. That most of these cases of intussusception are of the ileocecal type suggests very strongly some anatomic factor as a probable predisposing cause and that some operative procedure, if possible, ought to be established to prevent recurrence.

I am indebted to the visiting surgical staff of Lebanon Hospital for permission to report hospital cases.

American Journal of Diseases of Children

CONCERNING THE NATURE OF "PROTOZOAN-LIKE" CELLS IN CERTAIN LESIONS OF INFANCY [*]

ERNEST W. GOODPASTURE and FRITZ B. TALBOT

BOSTON

The so-called "protozoan-like" cells with which this paper is concerned were first described in 1904 by Jesionek and Kiolemenoglou,[1] who found them in the kidneys, lungs and liver of an eight months fetus, in intimate association with lesions of hereditary syphilis. The authors pictured these extraordinary structures as measuring on an average from 20 to 30 microns in diameter, usually oval in outline, possessing a well defined, though not sharply stained, cuticular zone having the appearance of a capsule. The nuclei were large, eccentrically placed, each containing a very pronounced "central nuclear body" surrounded by two well defined zones, an inner dark and an outer clear zone. The entire nucleus appeared separated from the cell body by a membrane. In the clear outer zone of the nucleus were found spherical, darkly staining granules of different sizes averaging 1 micron. The width of the nucleus, inclusive of the membrane, measured 10 microns. The cell-body contained many granules, especially numerous at the pole opposite the nucleus, while nearer the nucleus were spherical vacuoles. Cells of this description were found in greatest numbers in the kidneys, occurring characteristically in groups of from ten to forty, lying in the interstitial tissue of the midzone where syphilitic inflammatory changes were most in evidence. None was observed either in glomerulus, tubule or blood vessel. In the lungs and liver similar cells were present, usually singly, at most in groups of four. Those in the lungs were situated in alveoli and bronchi, as well as in inflammatory interstitial tissue.

This publication induced Ribbert[2] shortly afterward to record observations on a similar case, also a syphilitic infant, which he had

1. Jesionek and Kiolemenoglou: Ueber einen Befund von protozoënaritgen Gebilden in den Organen eines hereditärluetischen Fötus, München. med. Wchnschr. **43**:1905. 1904.

2. Ribbert: Ueber protozoënartige Zellen in der Niere eines syphilitischen Neugeborenen und in der Paroti von Kindern, Centralbl. f. Allg. Path. u. Path. Anat. **15**:945, 1904.

studied twenty years previously, and failing an interpretation, had put aside. In the kidneys only of this infant he found unusually large cells, which evidently corresponded to those described by the previous authors. They lay in great masses within the lumina of nearly all convoluted tubules, never outside in interstitial tissue, nor in straight tubules and glomeruli. They filled the lumen, distended it and pressed the epithelium out flat about them. Here and there the epithelial cells were pressed apart by the "foreign" cells whose protoplasm extended to the membrana propria. The large cells possessed a round or oval homogeneous nucleus with a relatively voluminous, likewise homogeneous but not in all cases visible intranuclear body. The nucleus was separated from protoplasm by a clear zone, giving an impression as if its substance had contracted from the nuclear membrane. Ribbert's sections from this case were old, not well stained, and cellular details he admits were not so clear as might have been wished. In the same paper, he mentions two instances in which he found similar cells in the parotid gland of infants, one 3 months, the other 1 year of age. In these two there was no suspicion of syphilis. Only the parotid glands were studied, and in them characteristic large cells occurred only within ducts, singly or in groups.

In 1910 Smith and Weidman [3] discovered similar large cells in a stillborn fetus. The infant was not syphilitic and weighed seven and one-half pounds. The cells were present in sections of lung, liver and kidney, and not associated with any observed lesion, except minute foci of lymphocytes and polymorphonuclear leukocytes in the renal cortex and liver. The large cells were in groups in the kidney, always in renal tubules, either within or without inflammatory foci. In the liver one such cell was seen within an inflammatory focus. In the lung no inflammatory process was observed, but a number of separate large cells were found always within alveoli.

In 1915, these authors recorded a second case in which cells of the same character were present in an infant 2 months of age, regarded clinically as syphilitic, though this diagnosis was not confirmed by history nor by a positive Wassermann test. The infant died of a subacute organizing bronchopneumonia, and the large cells were observed only in the lungs. They were scattered among cells of inflammatory origin, never aggregated, and occurred only sparsely distributed throughout the section. There was a chronic interstitial pancreatitis, but no similar cells were seen in this organ.

---

3. Smith, A. J., and Weidman, F. D.: Infection of a Still-Born Infant by an Amebiform Protozoan (Entameba Mortinatalium, n. s.), Univ. Penn. Med. Bull. **23**:285, 1910. Further Note on the Occurrence of Entamoeba Mortinatalium as a Human Parasite, Am. J. Tropical Dis. & Prev. Med. **2**:256, 1914.

The above records are the only observations on these peculiar structures in human pathology which we have been able to find in the literature, and each observer has regarded them as possibly protozoan in nature. Smith and Weidman definitely classify the cells as endamebas and have given them the name *Endamoeba mortinatalium*. It would seem almost incredible that the condition could be one of protozoan infection confined to fetal and infantile life, and yet the large cells have appeared so unlike any tissue cell that previous observers have leaned toward this rather improbable interpretation. In none of the above instances has any evidence been presented of a possible histogenous origin. Jesionek and Kiolemenoglou submitted their preparations to the eminent protozoölogist Richard Hertwig, who thought the structures might represent a kind of gregarine. Ribbert sought the opinion of the biologists, Ehlers and Rhumbler, who would not commit themselves definitely, but stated that no morphologic criteria were absolutely against the protozoan character of the cells. Smith and Weidman state "it cannot be seriously thought that these cells are other than protozoan parasites" and proceed to classify them as *Endamoeba mortinatalium*.

The case which we shall describe is of especial interest in that it furnishes definite evidence of the histogenous origin of these cells, shows their transportation through the blood stream, and indicates that this peculiar cellular change is a retrogressive one by which certain cells become independent of the body tissues and capable perhaps of wandering about exhibiting a certain similarity to protozoa.

REPORT OF CASE

History.—C. D., was first seen Nov. 6, 1919, at the age of 6 weeks. Two children had previously died at about the age of 3 months of a disease which the mother says was similar to the present trouble. One child, aged 2 years, is strong.

Fourth pregnancy, full term, birth weight 9 pounds. Always breast fed. Thighs were raw at three weeks but healed up rapidly with white ointment. Ever since birth has had green stools. Day before coming in feet swelled up. During the past two days the child has had no appetite. Nurses normally but acts now and then as if there was considerable mucus in throat.

Physical Examination.—His physical examination showed a fat, pale baby, which looked puffy. Anterior fontanel was open and level. Pupils were equal and reacted to light. Mouth and throat normal. There was no enlargement of peripheral lymph nodes. Heart and lungs were normal. Liver and spleen were not felt. Knee jerks equal and normal. There was no Kernig sign. Scattered over the buttocks, legs and abdomen there was a superficial rash which was characteristic of a napkin rash. The urine at this date contained a marked trace of sugar with Benedict's solution, no albumin. November 9 and 11 the urine gave a precipitate with Benedict's solution. No acetone. The stool was a characteristic one of a normal breast fed infant and contained a large excess of fat. This, however, is not abnormal.
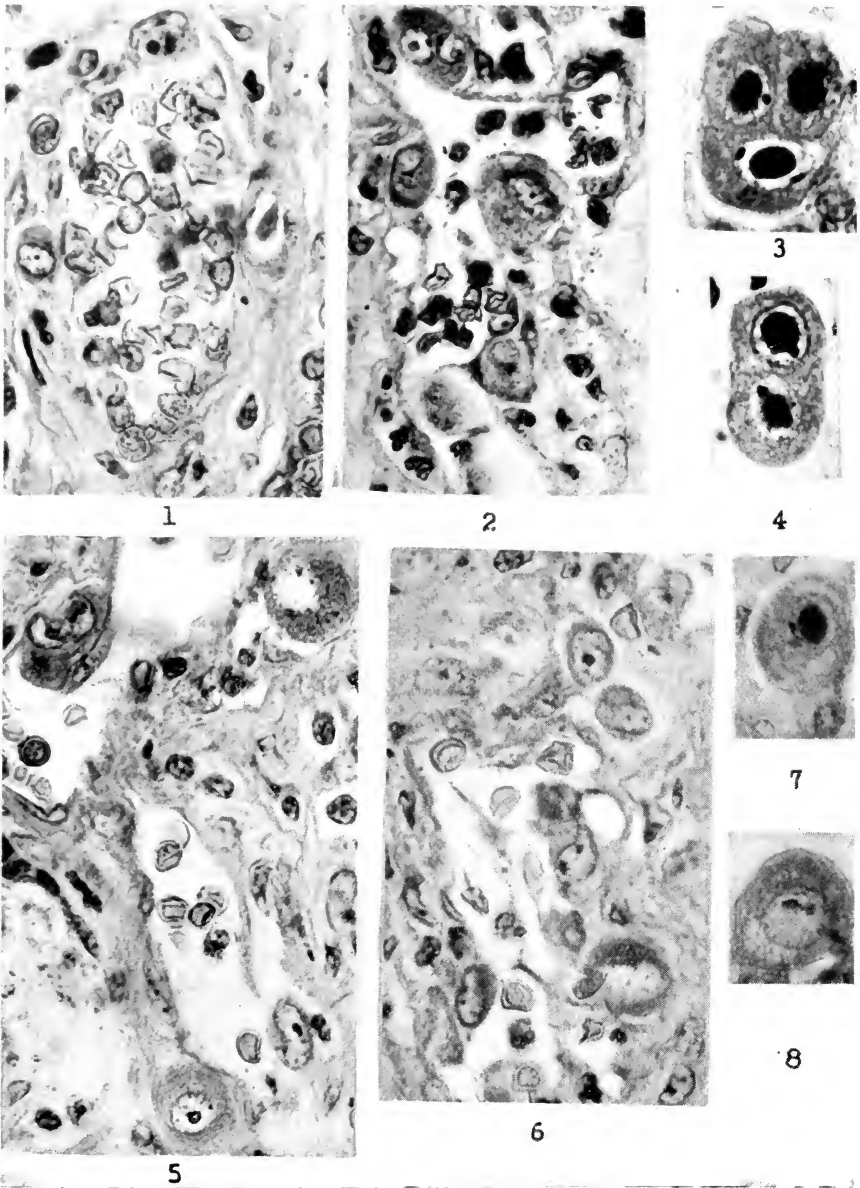
Fig. 1.—Transition forms of large cells in wall of bronchial vein. Note variation in size of dark intra-nuclear bodies. Cell in right wall has large clear nucleus, dark irregular intranuclear body. All photographs same magnification, Zeiss 2 mm. oil immersion objective, No. 2 eye-piece.

Fig. 2.—Transition forms of large cells, in wall of bronchial vein.

Fig. 3.—Group of three large cells in alveolus of lung.

Fig. 4.—Single large cell in alveolus of lung with horse-shoe shaped nucleus and intranuclear body, giving in section the appearance of double nucleus.

Fig. 5.—Transition forms of large cells in wall of bronchial vein.

Fig. 6.—Transition forms of large cells in wall of bronchial vein.

Fig. 7.—Large cell showing spherical bodies in cytoplasm.

Fig. 8.—Disintegrating form of large cell.

The analysis of the mother's milk November 13 showed: Fat, 2 per cent.; lactose, 7.2 per cent.; protein, 1.4 per cent. November 18 it was noted that the baby had been edematous, the edema extending up the legs to the abdomen.

The urine at that date showed a reduction with Benedict's solution after boiling in a water bath for five minutes. When the urine was kept for any length of time it did not show any reduction with Benedict's solution. November 19 the reduction was found again with Benedict's solution and negative with phenalhydrazin test. At no time did the urine contain acetone or diacetic acid. On this date there were many pus cells in the sediment. The renal function test (phenolphthalein) showed 35 per cent. The baby's blood sugar was 9.4 mg. per 100 c.c. of blood. The baby's blood urea $N = 26$ mg. per 100 c.c. of blood.

Baby died a few days later. Edema, cough and loss of appetite being the prominent features on the third to fourth day preceding death.

Wassermann reaction on mother's blood was negative.

Necropsy.—Eight hours postmortem.

External Examination: The body is that of a 2 months old white male infant. There is very marked pallor. Considerable edema of feet, legs and hands. Abdomen is greatly distended, evidently by intestinal gas. Pupils equal, mucous membranes pale. No discharge from ears or nose. No eruption present. The body is poorly nourished.
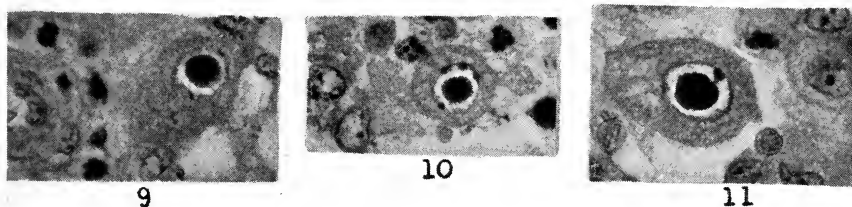
Fig. 9.—Large cell lodged in capillary of liver.
Fig. 10.—Large cell free in bronchial lumen in midst of cellular exudate.
Fig. 11.—Large cell in alveolus of lung, showing reticular cytoplasm.

Peritoneal Cavity: On opening the abdominal wall very little subcutaneous fat is found. Both small and large intestines are greatly ballooned with gas. Peritoneal surfaces are smooth, shiny, and moist. No evidence of inflammation. Organs are normally situated. The liver is very large, pale, yellow and fatty. Spleen perhaps slightly larger than normal. No marked enlargement of lymph glands. Pancreas is small, granular, firm and white. No excess of peritoneal fluid.

Thoracic Cavity: No excess of fluid in either pleural cavity. The lungs are voluminous, and both lower lobes completely consolidated. There is a little translucent, granular fibrin in places over these lobes. Pericardium is normal. Heart appears normal. Thymus small.

Lungs: Both lower lobes are quite similar in appearance. They are voluminous and completely consolidated. The margins are thin and delicately frayed, but the delicate filaments are not fibrin, being tough and adherent. The posterior portion of the apices are purplish in color, the remainder of the lobes pale grayish yellow. The pleural surfaces are smooth, and no fibrin is detected with certainty. The two upper lobes, and the middle lobe, show some pale edema posteriorly, and a few small hemorrhagic areas here and there, but no diffuse consolidation. They are air containing, and somewhat emphysematous, but no ruptures or bullae are found.

On section through the lower lobes the bronchi are seen to be dilated and filled with plugs of yellow pus. Even the smaller branches are dilated and pus-containing. The bronchial walls appear thickened. The intervening alveoli are filled with exudate and appear pale and yellowish. The entire lobe is fairly firm, but pus can be expressed with little pressure, and the gross appearance is that of a subacute confluent broncho-pneumonia, lobar in distribution, with purulent bronchitis and bronchiectasis.

Heart: Myocardium and valves appear normal.

Intestinal Tract: Stomach and intestine appear normal, except for postmortem softening of mucosa and distention with gas. Mesenteric lymph glands not enlarged.

Spleen: Perhaps slightly larger than normal, reddish purple in color, fairly firm and malpighian bodies not especially conspicuous.

Liver: Very much enlarged, capsule tense and smooth, pale and yellow. Cut surface greasy; lobulation rather indistinct; cut surface uniform. Appearance is that of very marked fatty change. Gallbladder and ducts appear normal.

12   13   14
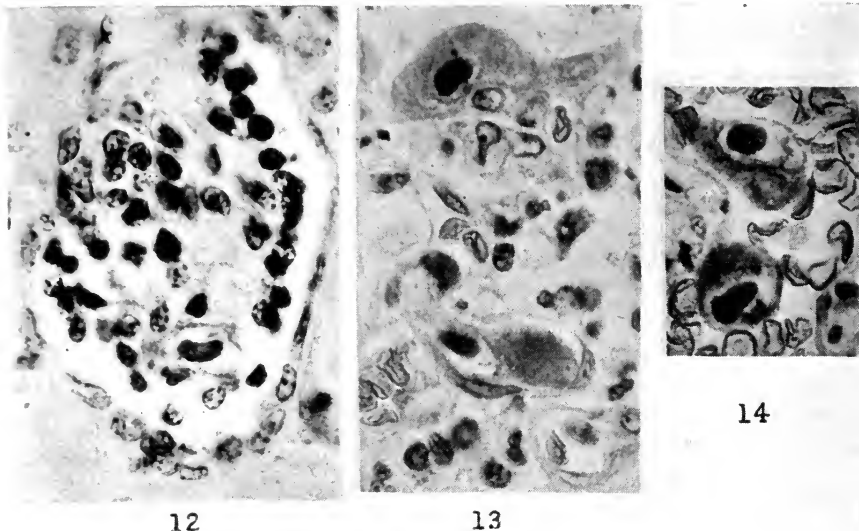
Fig. 12.—Large cell lodged in capillary of renal glomerular tuft. The cell is situated at lower pole of tuft and shows well the clear nuclear space and dark oblong intranuclear body.

Fig. 13.—Large cell filling capillary of lung alveolus (lower). Upper, large cell partially lines alveolar wall.

Fig. 14.—Two large cells free within vein of bronchial wall.

Pancreas: Is small, white, firm and granular. There appears to be a diffuse increase of interlobular, and interacinar connective tissue and atrophy of parenchyma. Ducts not dissected out.

Kidneys: Appear larger than normal, pale and moist. Capsule strips easily and leaves a smooth, pale uniform surface. Cut surface shows a thickened cortex, somewhat more opaque than normal, but with regular striations and architecture.

Suprarenals: Appear normal in gross.

Urinary Bladder: Contains clear urine, about 50 c.c. in amount. The pelvic organs show no obvious pathological change in gross.

Microscopic Examination. — The pancreas microscopically shows fibrosis and dilatation of ducts. Numerous islands are found and they appear normal. Glycogen is not present in the liver, but occurs in considerable quantity in the ascending loops of Henle in the kidneys.

Stained sections of heart, lungs, liver, pancreas, kidneys and suprarenals by Levaditi's method show no spirochetes.

Microscopic examination of the lungs shows a subacute bronchopneumonia in both lower lobes. The mucosa of most terminal bronchi in these lobes is partially or completely ulcerated containing a polymorphonuclear exudate mixed
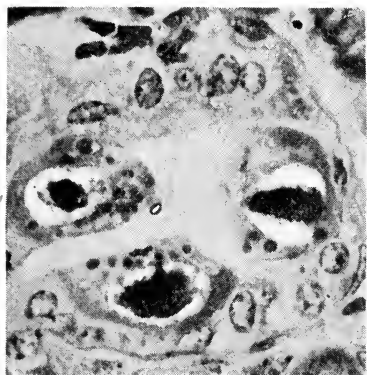
15   16
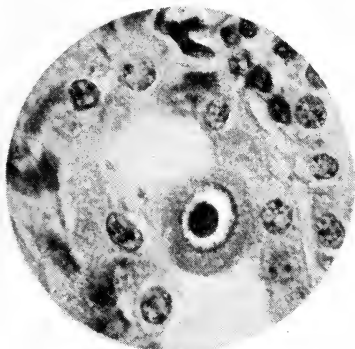
17   18

Fig. 15.—Large cells in epithelial wall of serous salivary gland of guinea-pig. Note dark irregular intranuclear body, clear nuclear space and spherical bodies in cytoplasm. Such spherical cytoplasmic bodies were very prominent in case reported by Jesionek and Kiolemenoglou.

Fig. 16.—Large cell partially lining alveolar wall of lung. Opposite it are epithelial cells containing enlarged acidophilic intranuclear bodies.

Fig. 17.—Large cell free in convoluted tubule of kidney.

Fig. 18.—Group of three large cells between renal tubules.

with some fibrin and cellular debris. The bronchial walls are thickened by edema, an exudate of mononuclear cells and by fibroblasts. The smaller veins and capillaries are dilated. Neighboring alveoli are often compressed or filled with cellular exudate in which a few streptococci are present. There is an irregular consolidation of intervening alveoli by purulent exudate, a little fibrin

and desquamated epithelial cells. Irregularly distributed throughout the inflamed lung are a great many large cells conforming in appearance to the descriptions of the protozoan-like cells given by the above mentioned observers. These cells are present most numerously within the walls of chronically inflamed bronchi, but are to be seen also in considerable numbers within the epithelial lining and free in the lumina of alveoli. They are usually round or oval in shape, but may be elongated and irregular in outline, depending on their situation. Those within alveoli are more likely to be round or oval, while those in bronchial walls may be quite irregular. They measure from 10 to 30 microns in diameter. No distinct cellular capsule, as described by Jesionek and Kiolemenoglou is to be seen. Each cell contains a very large nucleus separated from the cytoplasm by a sharp membrane. In the center of the nuclear area is a large acidophilic body which sometimes appears dense and homogeneous, sometimes delicately honey-combed. It may have a central denser portion with a lighter periphery. There is a clear unstained space between the central nuclear body and the nuclear membrane in which usually are seen dark, dense, basophilic, often spherical granules, only two or three of which are to be seen, as a rule, in a single section through the cell. One may be situated at each pole of the central body, or they may be irregularly arranged about the nuclear membrane. The cytoplasm of these cells is variable in appearance. It is more basophilic than neighboring tissue cells, may be reticular or may contain rather large spherical basophilic granules or vacuoles. Usually eosin staining granules and thin rods can be seen within it in preparations stained by the eosin methylene blue method after fixation in Zenker's fluid.

COMMENT

One observing well developed cells of this type, can hardly recognize a resemblance to any normal cell of the body, but within the walls of the bronchi in these lungs it can be readily seen that they arise from a metamorphosis of certain tissue cells which lie just outside the endothelial lining of small veins and capillaries. These perivascular cells belong to the group of so-called "large mononuclear wandering cell," and are probably derived in this case from endothelium. They possess an oval or slightly horse-shoe shaped vesicular nucleus and a reticular lightly basophilic nongranular cytoplasm. The first evidences of change in them is the appearance of a small eosin-staining intranuclear body having characteristics of a nucleolus. The nuclear chromatin aggregates and the nuclear mass seems clear and empty. Coincidently the cell increases in size and the cytoplasm takes a more deeply basic stain. Sometimes eosin-staining granules or fine rods can be seen in the cytoplasm. The central nuclear body continues to enlarge, and with it the nucleus and cell body greatly increase in size until they become relatively huge. The nucleus may be horse-shoe shaped, containing an elongated, similarly shaped, intranuclear body. Cells at this stage of change appear sometimes partially to line a small vein or they may be entirely free within the vascular lumen, occasionally completely filling a capillary. Likewise they may occur between epithelial cells of a bronchus or within a bronchial lumen. They are usually single, but may be in groups of three or four, especially in alveoli.

Evidently after gaining entrance to the blood stream through the endothelium of bronchial veins they are carried in the blood current to the kidney where they can be found here and there lodged within glomerular capillaries. That they can in some way penetrate capillary walls is indicated by their occurrence also within convoluted renal tubules where they lie free within the lumen. Occasionally, one or two are found in the interstitial tissue outside a tubule which contains similar cells. There is no inflammatory reaction about them in the kidney. An occasional cell of this type is seen in the liver in a portal area, probably having been borne there through the blood stream and lodged within a capillary. No inflammatory reaction is present in the liver. No cell of this type has been observed in organs other than lung, kidney and liver.

The origin of the cellular change in the lung seems to be directly related to the chronic inflammatory process in bronchial walls. In areas of more acute inflammation such cells are not found. In most of the cases previously reported there was also an associated chronic lesion, three instances of possible congenital syphilis and one of pneumonia quite similar to that described here. The cause and significance of this singular metamorphosis is not clear, but it is apparently a retrogressive manifestation, for many such cells can be seen to be disintegrating, and there is no evidence whatever that multiplication can take place. The great size of the cells at first suggested the possibility of their origin from megakaryocytes, but in capillaries within areas of more acute pneumonia normal bone marrow giant cells were found; and the cells under consideration have no likeness or relation to them.

While it is clearly evident that certain perivascular tissue cells in the bronchial walls become transformed into the so-called "protozoanlike" structures, it is not certain that all of them are derived from this source. The possibility of other types of cell, particularly epithelium, undergoing a similar transformation should not be ignored. Occasionally, one can see changes in nuclei of alveolar epithelium in the above described lung which suggest that they too may be undergoing the same alteration of character. Certain of these epithelial cells contain large eosinophilic intranuclear bodies surrounded by a clear zone, but no undoubted examples of transition have been observed. The two instances recorded by Ribbert in which the large cells were present within ducts of the parotid gland without evidences of inflammation also suggest the possibility of such an epithelial transformation. Recently Jackson[4] called attention to certain structures occurring within epithelium lining ducts of salivary glands of guinea-pigs, which we have little hesitation in saying are examples of a cellular transformation

4. Jackson, L.: J. Infect. Dis. **26**:347, 1920.

similar to that occurring in the above described lesions of infancy, although they were regarded by her as protozoan parasites. We have studied a number of our own preparations of salivary glands from apparently normal guinea-pigs which contain these bodies, and while there are minor differences of structure, the change appears to be essentially the same as in the lesions of infancy. We have observed them only within ducts of serous glands, and there may or may not be an attendant focus of mononuclear cells near. There is no evidence of transition of epithelium lining the ducts, but when these cells are regarded as altered tissue cells and not protozoan parasites, the possibility of their origin from epithelium becomes obvious.

It is difficult to formulate an opinion as to the nature of this remarkable cellular change. The earliest recognizable alteration in the transition forms is the prominence of the acidophilic intranuclear body which in well developed stages becomes perhaps the most conspicuous structural component. A somewhat similar structural variation in the intranuclear body has been described by Tyzzer [5] in cutaneous lesions of varicella. In the region of epithelial vesicles the intranuclear bodies of different varieties of cell, including epithelium and endothelium, becomes very prominent and resembles in certain respects those found in early stages of the protozoan-like cells. Certain cells thus affected may enlarge and through amitotic division become multinucleated. Influenced largely by the structural prominence of the intranuclear body in the large cells of the infant's lung, one is tempted to suggest that the nucleolus may be the site of the initial change and under its diseased influence the cell as a whole may change in structural properties.

In the above described lesions of the lung the large cells appear to be secondary to the subacute pulmonary inflammation and apparently are a result of it. There is a possibility also that in the other recorded cases their occurrence was secondary to inflammatory changes of one sort or another. That their appearance in any way influenced the intercurrent disease does not seem at all probable. The arrested development and fibrosis of the pancreas, the glycosuria and renal functional disturbances do not seem to be in any way directly connected with the cellular anomaly.

Demonstration of the origin of these unusual structures from tissue cells adds to pathology a new kind of abnormal cytomorphosis, manifested by morphologic peculiarities entirely unknown in adult human lesions. Cellular gigantism is familiar in certain tumors, but not even the many morphologic vagaries of cancer have simulated the structure of these abnormal cells of infancy.

5. Tyzzer, E. E.: The Histology of the Skin Lesions in Varicella, Philippine J. Sc. **1**:4, 1906.

While the conspicuous character of these cells may cause them to dominate the microscopic picture, their presence hardly indicates a disease entity, but rather they seem to represent an effect of chronic inflammation upon certain cells which may not be so stable in infancy as in adult life. The possibility of an unknown intracellular infection stimulating the cells to assume this unusual structural variation has at present no evidence to support it.

This cellular change is of such a characteristic nature that there is no difficulty in recognizing it when present, but as heretofore it has not been recognized as a metamorphosis of tissue cells, it seems advisable to identify the condition with a descriptive name, and we would suggest that it be called *cytomegalia* to emphasize the notable enlargement of the cells affected, and at the same time to distinguish it from those forms of cellular enlargement which at present are included under the general term giant cells.

REPORT ON A CASE OF GAUCHER'S SPLENOMEGALY *

N. CHANDLER FOOT, M.D., and WILLIAM E. LADD, M.D.

BOSTON

Up to the present time only twenty-one cases of this unusual disease have found their way into the medical literature. First described by Gaucher,[1] in 1882, it was not mentioned again until 1895, when Picou [2] published his first article, followed by a second,[3] in conjunction with Ramond, in 1896. Collier,[4] in England, had, in the meantime, published a report in 1895. Bovaird [5] was the first to describe it in America, and it was only in 1906 that Schlagenhaufer [6] reported the first German cases. F. S. Mandelbaum, of New York, has undoubtedly done the most to put the pathologic peculiarities of the disease on a sound footing.[7] Working alone and with various collaborators, notably Brill (who published two articles independently [8]) and Downey, he has given a most comprehensive survey of the clinical and pathologic aspects of these cases.

According to him, the disease occurs oftenest in childhood, may be familial, is accompanied by progressive enlargement of the spleen (which may attain colossal proportions) and is followed by a similar enlargement of the liver. There are frequently brownish-yellow discolorations of the face, neck and hands, wedge-shaped thickenings of the conjunctiva, like pinguecula, usually beginning on the nasal side and appearing later on the temporal, their apices at the outer rim of the cornea. The disease has a prolonged, chronic course, with surprisingly little disturbance of function. Later, there may be a tendency toward

---

1. Gaucher, E.: De l'épithéliome primitif de la rate, Thèse de Par., 1882; Sémaine méd., 1892, p. 331; La France méd., 1892.

2. Picou. R.: Bull. de la Soc. anat. de Par., 1895, p. 531.

3. Ibid and Ramond. F.: Arch. de méd. expér. et d'anat. path. **8**:168, 1896.

4. Collier, W. A.: Tr. Path. Soc. Lond. **46**:148, 1895.

5. Bovaird, D.: Am. J. M. Sc. **120**:377, 1900.

6. Schlagenhaufer, F.: Virchows Arch. f. path. Anat. **187**:125, 1907.

7. Brill, N. E.; Mandelbaum, F. S., and Libman, E.: Am. J. M. Sc. **129**:491, 1905; Brill, N. E., and Mandelbaum, F. S.: Am. J. M. Sc. **146**:213, 1913; Mandelbaum, F. S.: J. Exper. M. **16**:114, 1912; Mandelbaum, F. S., and Downey, H.: Bull. Johns Hopkins Hosp. **27**:109, 1916; Mandelbaum, F. S., and Downey, H.: Folia Hemat. **20**:139, 1916; Mandelbaum, F. S.: Am. J. M. Sc. **157**:366, 1919.

8. Brill, N. E.: Am. J. M. Sc. **121**:377, 1901; Proc. New York Path. Soc. **4**:143, 1904.

bleeding from the nose, bowel or uterus; leukopenia, and, ultimately, anemia of the chlorotic type. Occasional symptoms are persistent sweating and abdominal pain or pain in the legs. Females have been more affected than males, although more male cases have been reported recently, which has somewhat altered the ratio.

The disease is very insidious in its onset, slight dragging pain or enlargement of the spleen may be the first symptoms noted. The average blood count shows: Hemoglobin 65 per cent., (from 35 to 92 per cent.); erythrocytes, 6,000,000, later 3,700,000; leukocytes slightly decreased. Differential count: Polymorphonuclears, 66 per
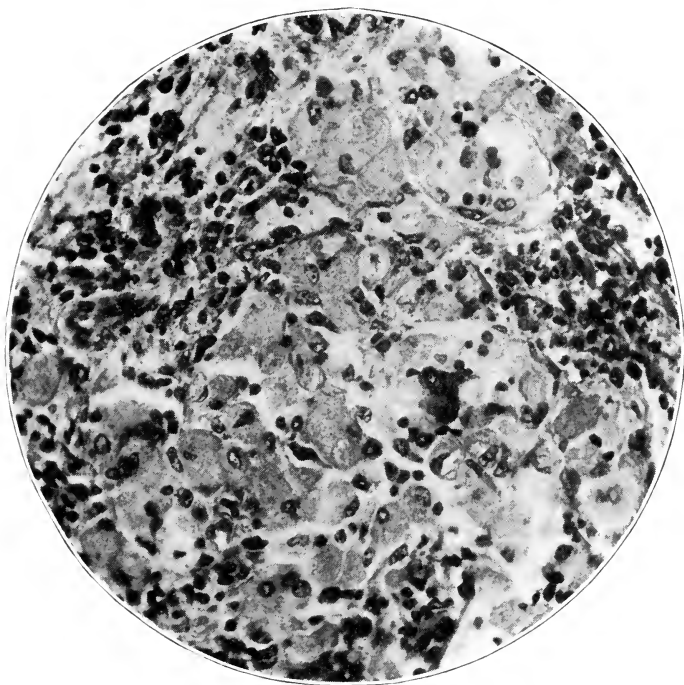
Fig. 1.—Paraffin section, phosphotungstic acid-hematoxylin, × 400. Gaucher cells in their usual alveolar arrangement. Note vacuoles and striae in several.

cent.; macrolymphocytes, 13 per cent.; microlymphocytes, 20 per cent.; eosinophils, 1 per cent.; mast cells, from 0.5 to 0.8 per cent. The large cells peculiar to the disease are never found in the circulating blood; there are no nucleated red cells. The duration is 19.3 years on the average, it may be much longer, the patient usually dying from some intercurrent infection.

Pathologically speaking, the disease is limited to the hematopoietic system; beginning in the spleen, it spreads to the regional lymph nodes of the mesentery and retroperitoneal groups, involves the bone marrow

and appears in the radicles of the portal vein and in the perilobular connective tissue of the liver, where it is, therefore, confined to Glisson's capsule. The spleen is usually much enlarged, it may extend from the diaphragm to the left iliac fossa. It is usually smooth, firm and apt to show one or more deep notches in its anterior margin. On section, the color is generally pale, grayish pink with minute, semitranslucent areas about 1 mm. in diameter scattered uniformly over the cut surface. Often there are hemorrhagic areas of small size. Rarely, there is evidence of necrosis, but only where tuberculosis
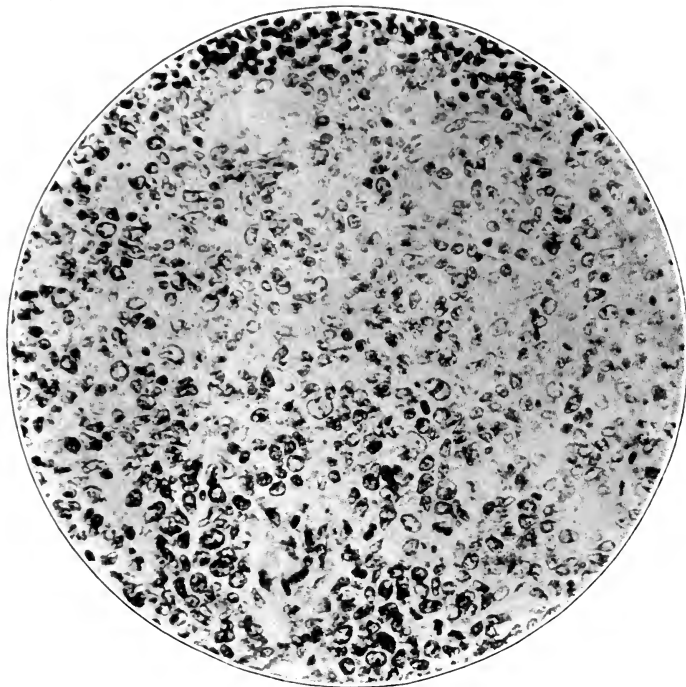
Fig. 2.—Paraffin section, phosphotungstic acid-hematoxylin, ×400. A "germinal center" from the spleen, showing several mitotic figures, and near 2 o'clock, three "tingible Körperchen" in a cell.

was associated with the lesions (Schlagenhaufer, loc. cit.). The liver is enlarged, and on section shows a fine network of pale, slender strands running between the lobules and outlining them in grayish-white. It is brownish in general tone and cuts with increased resistance. The lymphnodes of the mesentery and retroperitoneal region are enlarged and pale, and, on section, show a picture somewhat similar to the cut spleen. The bone marrow is grayish-red and thickly strewn with tiny, whitish specks, similar to those seen in the spleen and lymphnodes.

The microscopic picture is similar in all these organs; there are a great many large ovoid cells with small nuclei and somewhat vacuolated cytoplasm, usually lying in venous or lymphatic sinuses, or in the meshes of the tissue in question. They will be described at length later on, in the cases of the spleen; they are discussed in great detail in connection with the other organs involved, in any of the longer articles referred to in the list of references given in this paper.

Our case occurred in a boy, aged 8 years, who was admitted to the Children's Hospital suffering from persistent sweating, sudden loss in weight and anorexia. A mass was made out in his left hypo-
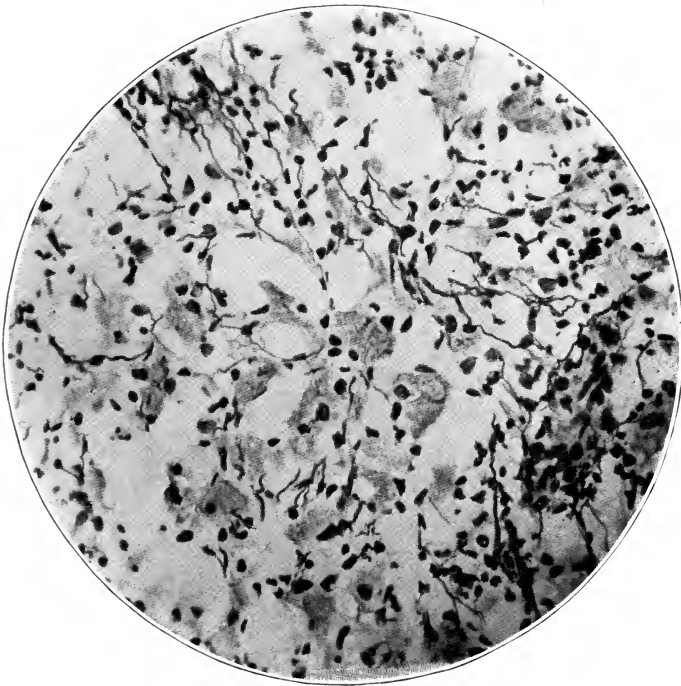
Fig. 3.—Frozen section, Bielschowsky-Maresch impregnation, × 400. Showing the delicate reticulum of fibrillae and the anastomosing Gaucher cells through which they run.

chondrium, but no definite diagnosis was arrived at until an accessory splenule, removed during an explanatory laparotomy, was diagnosed as typical of Gaucher's splenomegaly. It will be noted from the history that most of the typical symptoms were absent, while several of those usually considered occasional were present. These facts, together with the vague history of gastro-enteric disturbances and epileptoid seizures, made the clinical diagnosis of the case extremely difficult.

REPORT OF CASE

History.—The patient, Albert B., 8 years of age, was admitted to the surgical service in May, 1920. His anamnesis is compiled from data given by the parents at this time and from notes made by various observers in the Outpatient Department, where he had been an occasional visitor since 1915.

Family History.—His family history is negative; his parents and five brothers are alive and well, no deaths, no tuberculosis, cancer, insanity, nor hemophilia.

Previous History.—Birth normal, breast-fed. Between the second and fifth years of his life he had five attacks of unexplained unconsciousness, diagnosed by the neurologists as "probable epilepsy." He was first brought to the Outpatient Department in January, 1915, and again in June of that year. Both times the complaint was loss of weight, anorexia and restlessness—particularly
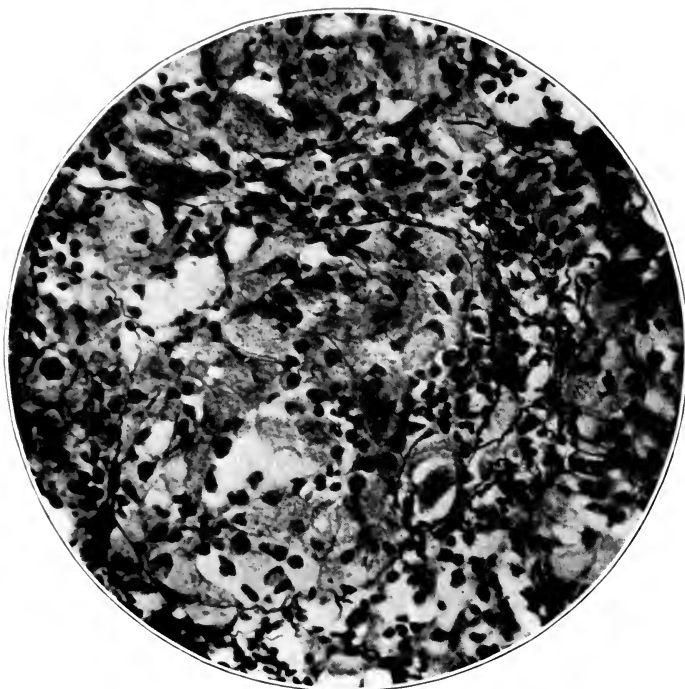
Fig. 4.—Thicker frozen section, Bielschowsky-Maresch impregnation, ×400. Showing alveoli and also the anastomosing type of arrangement of the Gaucher cells. Note the coarse, undulating fibrils of the more normal pulp reticulum and the straighter, finer fibrillae of the Gaucher cell cytoplasm.

at night. Diarrhea was the outstanding symptom at the second visit. In July, 1916, he had lost 3 pounds in weight and was suffering from "feverishness" and severe headaches. He had had two of his unconscious spells since the preceding visit and had had chickenpox. A fulness of his left flank was noted on physical examination at this time.

He was not heard from again until September, 1918, when he came back with a history of persistent vomiting and poor appetite. In May, 1919, he was suffering from profuse sweating, both at night while in bed, or in the daytime after the slightest exertion. He had severe frontal headaches daily, most severe

in hot weather, was nauseated, but did not vomit until the day before he was brought in. He had night terrors and was very irritable. On physical examination his spleen was palpable 1 cm. below the costal margin, in the nipple line.

In June, 1919, he was re-admitted, suffering from traumatic synovitis of the knee, which was noticeably stubborn. At that time his spleen was noted as being "just palpable." In September, 1919, an irregular, doughy mass, feeling more like impacted feces than a spleen, was palpable in his left hypochondrium. This was apparently unconnected with the spleen, as it could be rolled under the fingers, was freely movable and did not move with respiration. His liver was just palpable below the right costal margin. A blood count, made at this time, showed, hemoglobin, 80 per cent.; leukocytes, 9 600. Differential Count: normal.

Present Illness.—In April, 1920, he was examined at the Outpatients' Department and sent to the hospital. He had been feeling moderately well, but had just recovered from mumps and measles. His appetite was now very poor, he had pain in his entire body after playing, most marked in the abdomen, occasional morning vomiting and perspired excessively. When put to bed he would be restless and perspiring and would not go to sleep until late, sleeping late in the morning. He was not attending school on account of his extreme nervousness and his vomiting. He complained of seeing "colored balls" before his eyes and "having shocks" over his entire body. On admission to the hospital the chief complaints were sudden loss of weight and excessive perspiration.

Physical Examination.—On admission this was negative, save for a large, smooth, painless, movable tumor in the left hypochondrium. The dulness extended upward to the angle of the left scapula and 8 cm. to the left of the midsternal line. The tumor was palpable 4 cm. below the costal margin in the left nipple line. The left flank was fuller than the right. Shortly after admission the house surgeon noted: "Large tumor in left side; opinions differ as to whether this is spleen, kidney, or some neoplasm."

His blood count at this time showed: Hemoglobin, 90 per cent.; erythrocytes, 5,808,000; leukocytes, 6,600: Differential Count: Polymorphonuclears, 49 per cent.; macrolymphocytes, 19 per cent.; microlymphocytes, 30 per cent.; mononuclears, 3 per cent. One myelocytic neutrophil was noted. His von Pirquet test was positive but indefinite to bovine, negative to human tubercle bacilli. Wassermann was negative. His temperature was subfebrile, averaging from 99 to 100 F.

Treatment.—An exploratory laparotomy was performed May 10, 1920, revealing a large, smooth spleen and two accessory splenules, one of which was excised from the omentum and sent to the pathological laboratory. The report was "typical of Gaucher's splenomegaly." Accordingly, June 1, 1920, the spleen and the remaining splenule were removed. The patient made an uneventful recovery; the stitches were removed on the eleventh day and he was discharged the day following. He was seen Oct. 15, 1920, and found to have gained 8 pounds and to be much improved in health. His sweating had practically disappeared, his digestive disturbances were not marked, and he could attend school regularly. Just before his discharge from the hospital his blood count showed: Hemoglobin, 80 per cent.; erythrocytes, 4,976,000; leukocytes, 18,800. Differential Count: Polymorphonuclears, 48 per cent.; lymphocytes, 41 per cent.; mononuclears, 10 per cent., and eosinophils, 1 per cent. No abnormal red cells were present.

Pathologic Reports.—May 10, 1920. A small nodule, bright red in color, enclosed in a small mass of omental fat, resembled an accessory spleen; is lens shaped; measures 0.6 cm. in diameter and 0.4 cm. at its thickest portion.

Microscopic Examination: Rudimentary splenic tissue, with poorly defined trabeculae and splenic corpuscles. There are no nodules or marginal sinus, like those of a lymph node. The sinuses and pulp spaces of this little spleen are filled with large, vacuolated or reticulated cells, which contain occasional inclusions.

Operation.—The large spleen proper and the remaining accessory spleen were removed, June 1, 1920. The spleen weighed 305 gm. and measured 14 by 6 by 5 cm. It was markedly lobulated, with two distinct notches and a smooth capsule. Outwardly of an almost normal color (reddish-purple), it was pale, pinkish-buff on section. The cut surface was marked with small, semitranslucent masses about 1 mm. in diameter, and the splenic corpuscles stood out reddish on a pale background, the reverse of normal. The consistence was firm and rather waxy; the pulp did not strip on the knife edge. A smaller, accessory spleen accompanied the specimen. It was about the size of a small filbert, 1.5 by 1 cm. Its appearance, consistence and color, correspond to those of the larger organ.

Microscopic Examination of Spleen.—The microscopic architecture of the spleen was so strikingly altered by the interpolation of the large cells typical of this condition, that one would scarcely recognize it at first glance (Fig. 1). There were countless numbers of these cells everywhere, filling the venous sinuses and pulp spaces so completely as to transform the picture into one resembling an alveolar tumor. They vary from 17 to 35 microns in diameter and are roughly ovoid in shape; their cytoplasm is usually pale, but here and there one finds cells with a more homogeneous, deeply staining protoplasm. As a rule, however, they show a pale, reticulated structure with the fibrils running in a longitudinal and roughly parallel fashion, from pole to pole of the cell. They often contain inclusions of a hyalin nature, which will be described presently. The nuclei resemble those of the reticular cells, or of the endothelial cells, in that they are vesicular, show a delicate chromatin reticulum and one to three larger masses of basophil material, like nucleoli. In the eosin methylene blue sections prepared from this spleen, there is a tendency toward eosinophilia on the part of these nuclei, as is also the case with those of some of the reticular cells. The endothelial nuclei, in cells lining sinuses, do not show this, but stain deep blue.

Mitotic figures are extremely rare in the Gaucher cells; only one was found after prolonged searching. These cells fill both the venous sinuses and the pulp spaces so full that it is extremely difficult to tell the former from the latter. There are no such dilated sinuses with a comparatively clear lumen, filled mostly with erythrocytes, as pictured in most of the cases in the literature. The whole field, in our case, seems to be composed of irregular alveoli filled with large, pale reticulated cells. The inclusions just spoken of are in the form of hyalin masses or droplets in the cytoplasm of the Gaucher cells. They give practically the same staining reaction as does collagen: bright red with eosin methylene blue, brownish red with Van Gieson's stain and phosphotungstic acid hematoxylin sections, indigo blue with Mallory's anilin blue connective tissue stain, dirty to bluish green with Weigert's elastic tissue stain and blue with ferrocyanid of potash. In unstained section they are rather faint brownish yellow. They do not react with sudan III nor Nile blue. They are not confined to the cells, but lie about among them and apparently fill the cytoplasm of the smaller cells of the familiar endothelial phagocytic type, the nucleus being crowded to one side. Or, sometimes, no nucleus can be made out and the bodies appear like empty hulls; for this reason they seem, at first, to be artefacts, but after more careful study this does not appear to be so. They seem to exist, at first, as small branching masses of what looks, at first glance, to be fibrin; these gradually appear more swollen and hyalin and are taken up by the cells. The hull-like structures are probably the "shadows" of these cells after they have become necrotic; one often finds them badly wrinkled, or shriveled, their nuclei obviously in the last stages of karyolysis.

One occasionally finds erythrocytes which have apparently been phagocytosed by the Gaucher cells, lying in vacuoles in the cytoplasm of the latter; so many lie on, rather than in the cells, that this must be stated with reservations. There are also two forms of pigment in the cytoplasm of the Gaucher cells; a

very faintly yellow granular form and an apparently diffuse and almost invisible one, both of them containing iron in a free state. They scarcely would have been noticed in this case, if one had not read of them elsewhere and tested for them chemically. Two familiar lipoid stains were used to determine the presence of fat or lipoids in the Gaucher cells, but without success. Sudan III demonstrated no granules, and Nile blue, while staining some of the cells more deeply than others, gave no typically granular reaction. In the face of this evidence, there is no need for employing other and more complicated lipoid stains.

Having disposed of the description of these cells, little is left to say about the lesion; the splenic capsule and trabeculae are not much thickened, the amount of elastic fibers is apparently normal, there is no increase in connective tissue elsewhere in the organ. The malpighian corpuscles are, as a rule, small; they are not much altered, here and there one finds one with a larger, well developed germinal center (Fig. 2) which shows active mitosis among the macrolymphocytes. Occasionally, these cells are larger and more vesicular than usual and rarely one finds gigantic cells of this type with very large, somewhat lobulated, vesicular nuclei, as described by Mandelbaum and others. Gaucher cells, or cells similar to them, are found lying singly near the periphery of the centers and containing many small, basophile bodies (Flemming's "tingible körperchen," Mandelbaum[1]). Occasionally, the lymphoid reticulum is swollen and hypertrophic. In this case there are comparatively few Gaucher cells in the germinal centers.

There is a network of strands of more normal pulp between the alveoli of Gaucher cells. Here one finds a marked increase in eosinophil leukocytes, of both polymorphonuclear and myelocytic types. Plasma cells are abundant. Occasionally one finds typical megakaryocytes and cells somewhat resembling them, but more like the "Dorothy Reed" or "Sternberg" type of tumor giant cells of Hodgkin's granuloma. The endothelium of the venous sinuses tends to desquamate abundantly and to become very hydropic and swollen. There are many cells resembling plasma cells, only much larger and apt to have irregular, ameboid outlines. Their nuclei are of the lymphocytoid type, their cytoplasm dense and slightly basophilic. One cannot fit them into a transition-scale between lymphocytes and the Gaucher cells. This sums up the pathology of the spleen, that of the two accessory spleens is quite analogous.

DISCUSSION

Since Bovaird described his cases, no one has attempted to put the Gaucher cells into any category other than that of the endothelial cells; opinions have differed as to whether they are purely endothelial, or whether descended from the reticulo-endothelial cells. The trend has been steadily toward the latter derivation and, in our case at least, this seems justified. It has already been stated that their nuclei and those of the reticulum tended to slight acidophilia in the eosin methylene blue preparations and that the reticulum of the germinal centers seems swollen and hypertrophic. This is also true of the adventitial cells of the smaller arteries.

Fortunately, a portion of the spleen frozen and cut for the Bielschowsky-Maresch silver impregnation showed a somewhat earlier stage in the disease than did the others (Fig. 3). Here the large cells are arranged in columns, or branching rows and in some places they are found to be stellate and to anastomose with one another. In these sections there is more normal pulp present, and the malpighian

corpuscles show very little deviation from the usual form. Thin sections from these blocks show a delicate network of reticulum fibrils with the Bielschowsky-Maresch method (Figs. 3 and 4). These fibrils run through the cells and not over them, when found in the stellate, anastomosing type. In the alveoli they surround the Gaucher cells very intimately (Fig. 4). Risel [9] stated that the large cells could be disengaged from this network readily, by slight pressure on the coverslip. It was found, in our preparations, that very rough treatment, such as grinding the section between the coverglass and the slide with one's thumb and forefinger, was necessary to break up the tissue and, even then, many of the Gaucher cells remained sticking together in groups of three or more. Some of them did, indeed, come out clear and discrete; but many still showed coarse fibrils in their cytoplasm, or adhering to their periphery. Shaking up such sections with glass beads in glycerin, for an hour, failed to break out any but an insignificant number of these cells, although many leukocytes and lymphocytes were liberated. There is no doubt that the majority of these cells are firmly bound together by a fine reticulum. Whether they produce it or not is, at best, a matter for speculation and deduction, rather than an observed fact. The odds are, however, strongly in favor of reticular origin.

This case, then, fulfills the requirements as postulated by Mandelbaum and Brill.[7] The large cells contain no lipoids, they do contain iron compounds showing the typical reaction to potassium ferrocyanid; both diffuse and granular. The various inclusions described are all present here, except that no iron-free pigment is demonstrable. Reticulum fibrils are found in the younger, anastomosing Gaucher cells and the columnar arrangement described by Mandelbaum (in connection with lymphnodes) is found here in the spleen.

It is interesting to note that the clinical symptoms in our case are rare ones, rather than the more usual variety. There was no cutaneous discoloration, no tendency to bleed, little enlargement of the liver and no conjunctival symptoms. Enlarged spleen, pain in the abdomen and legs and profuse sweating were present. The blood counts were not particularly significant, and there was a long history of gastro-intestinal disturbances which might be referable to lesions in the lymphoid apparatus of that tract, but which must remain, for the present, problematical. There seems to be no other case in the family. The child's spleen was first enlarged and palpable when he was 7 years old, the disease making, therefore, greater strides in the last twelve months than in the preceding three years elapsing since a "full-

9. Risel, W.: Beitr. z. allg. Path. u. z. path. Anat. **46**:241, 1909.

ness in the left flank" was noted. The immediate results of the splenec-
tomy have been most encouraging; it remains to be seen how the case
will conduct itself as time goes on.

In a disease of such rarity and which runs so long a course, the
advisability of radical operation must, necessarily, be still debatable.
But if the theory is correct that the disease originates in the spleen
and then spreads to the lymph nodes, liver and bone marrow, it is
logical to bend our efforts toward making an early diagnosis and
resorting to splenectomy as soon as possible. If, on the other hand,
the enlargement of the spleen is a manifestation of some metabolic
change of which we are at the present time ignorant and which will
continue, in spite of the removal of the spleen, to affect the liver,
lymphnodes and bone marrow, it is obvious that we can not expect
a permanent cure from splenectomy. However, we know at the present
time that the disease is fatal if untreated, or if treated by any means
other than radical operation; we likewise know that splenectomy will
afford very marked temporary relief from symptoms and improvement
in general health. With these facts in view early splenectomy is,
therefore, the treatment to be for the present recommended.

The literature [10] on this subject is, as a whole, well written, and
almost any of the more recent articles will give the reader a good
description of the disease; those of a Mandelbaum, Schlagenhaufer and
Risel are the most complete. Several cases have been reported as
Gaucher's splenomegaly which were, in reality, of a different type and
due to lipoidemia. Among these are those of Knox, Wahl and
Schmeisser and De Lange and Schippers; the reasons for excluding
them, as well as the exact references, will be found in Mandelbaum
and Downey's article.[7]

When one comes to a consideration of what causes the disease,
there is very little to say. We do not even know what processes it
represents. Gaucher thought it an epithelioma. In the nineties it was
considered an endothelioma. Bovaird was the first to advance the
theory of its being due to some toxin of unknown origin, and Mandel-
baum, in his last article says: "The disease is evidently caused by some
disturbance of metabolism, the products may be of a combined protein-
lipoid nature, not to be grouped among 'extractives' and for which
no microchemical test has yet been devised." One might be tempted
to consider the process as a tumor of the reticular tissue, starting in the
spleen, spreading to the hematopoietic system in the lymph nodes
and bone marrow and metastasizing to the perilobular hepatic connective
tissue of Glisson's capsule. But there is too much evidence on the
other side of the argument and too many points against neoplasia to
permit one's siding with the earlier writers on this subject. The spleen

and lymph nodes are not involved locally, but the whole organ undergoes this change. The cells show no true metaplasia, there are extremely few mitotic figures and the normal structure of the organs affected is always in the background; there is no true replacement by new tissue. We must, therefore, fall back on Mandelbaum's hypothesis as the most tenable; it is unfortunate that the condition is so rare that more cases cannot be studied in a systematic fashion, particularly from the chemical standpoint.[10]

---

10. In addition to the references already given, the following are also of interest:

Bernstein, E. P.: J. A. M. A. **64**:1907 (June 5) 1915.

Erdman, J. F., and Moorhead, J. J.: Am. J. M. Sc. **147**:213, 1914.

Evans, F. A.: Proc. New York Path. Soc. **16**:114, 1916.

de Jong. R., and van Heukelom, J. S.: Beitr. z. allg. Path. u. z. path. Anat. **48**:598, 1910.

Marchand, F.: München. med. Wchnschr. **54**:1102, 1907.

Reuben, M. S.: Am. J. Dis. Child. **5**:28 (Jan.) 1912; ibid. **8**:336, 1914; ibid. New York M. J. **107**:118, 1918.

A CASE OF IDIOPATHIC HEMORRHAGIC SARCOMA OF KAPOSI *

STAFFORD McLEAN, M.D.

NEW YORK

In 1872, Kaposi brought to notice an unusual and remarkable affection of the skin which was characterized by the occurrence of deeply pigmented infiltrated areas and small tumors situated generally in the extremities and often followed after several years by visceral metastases and death. Since then, many reports of cases have been published similar in certain aspects to Kaposi's type but characterized, on the whole, by wide variations from the original examples. In a search through the literature few cases in children have been discovered, and none of these are described in sufficient detail to invite comparison with the case herein reported.

The child was examined by a number of physicians, none of whom had seen a comparable condition in either a child or an adult. A variety of opinions were advanced regarding the probable diagnosis, but it was finally decided that it more nearly resembled the type described by Kaposi than any other.

REPORT OF CASE

R. B., 5½ years old, of Jewish parentage. Both mother and father were healthy and were born in the United States. The child was referred from the office of Dr. L. Emmett Holt Feb. 20, 1920, for admision to the Babies' Hospital and was under observation on his service for twenty-four days.

The patient was the third of three children; the others were apparently normal in every respect. Prior to the onset of the present illness the child had been healthy, well nourished and well developed. Seven weeks before admission to the hospital the child could walk freely, but had gradually become so weak that when seen in Dr. Holt's office he was only able to walk a few steps.

Previous History.—The father states that about seven months previously, a purple spot about the size of a thumb nail appeared on the left cheek. This grew very slowly, and at the end of three months it was about the size of a silver quarter, the color remaining the same. Shortly afterward the whole right cheek gradually became swollen and discolored. About six weeks after the spot was first noted on the left cheek, the father noted the appearance of other spots on the buttocks, hands, arms, legs, feet and body. He had observed that these spots had been appearing and disappearing to date. It has been further stated by the family that the swelling of the face had persisted since first observed but that at times it had been more marked than it was at the time of admission to the hospital. A few weeks after the onset of the disease epistaxis occurred and on another occasion there was a slight hemorrhage from the bowels.

The child had been treated at another hospital three months previously and while there received three transfusions. After the second transfusion the temperature rose to 106 F. and was accompanied by considerable swelling of the face.

Physical Examination.—On examination the child was found to be moderately well nourished and well developed. The mucous membranes seemed markedly anemic. Both cheeks were greatly swollen and hard and tense to the touch. There was a symmetrical deep purplish discoloration of the face not limited to the swollen cheeks but extending above to the lower lids and below to the lower lip and chin (Fig. 1.) On the left side of the face there was a marked induration extending from the cheek. It involved the cellular tissue of the whole of the left side of the face, extending as high as the external auditory meatus. This brawny area was also discolored, but the pigmentation was less intense than over the cheeks. A similar condition existed on the right side, but it was limited almost entirely to the right cheek with an isolated

Figure 1

patch in the middle of the supraorbital ridge. The lips were indurated and pigmented, particularly the lower, the induration was so marked that the child constantly kept the mouth partially open. The chin was discolored and indurated, but not to the same degree as the cheeks. There was a slight hemorrhage in the subconjunctiva of the left eye.

There were a number of subcutaneous masses, not sharply outlined, over the frontal region, and a few spots on the scalp about the size of a pea, all of which were purplish in color. The chest presented some faintly discolored

areas of a different character about the same size as those on the scalp, but these were not indurated. There were also a few spots on the upper chest and extensor surfaces of the arms and forearms which were apparently in the fading stage. Over the thighs and buttocks there were some spots similar in character to those on the chest and arms, one of which was indurated. The tonsils were hypertrophied, and a few hemorrhagic foci were noted on the tonsils and peritonsillar tissue.

All of the superficial lymph glands were slightly enlarged, but not tender on pressure.

Figure 2

A marked systolic murmur limited to the cardiac region was heard. It was evidently a hemic murmur. The apex beat was one-half inch inside the nipple line, the pulse rate was 136 and of fairly good quality. The abdomen was tympanitic with the distention mainly in the epigastrium. The lower border of the liver was felt about one inch below the costal margin and the lower pole of the spleen was one and one-half inches below the free border of the ribs.

Laboratory Examination.—The urine was found normal on several examinations, the Wassermann test was negative, the von Pirquet was negative and the guaiac test for occult blood in stools was negative on a number of occasions. The blood culture was sterile. The blood picture showed 25 per cent, hemoglobin, 1,288,000 red blood cells, with marked variation in size and shape. One nucleated red blood cell was present and a few irritation forms. The white blood cells numbered 2,400, and the differential count showed: polymorphonuclears, 21 per cent.; small lymphocytes, 52 per cent; large lymphocytes, 24 per cent., and eosinophils, 3 per cent. A number of blood examinations were made, each showing a progressive decrease in the total number of red cells, the count falling to 552,000 the day before death. The white count was not higher than 13,000 at any time, and at the last examination it was only 2,000. The coagulation time of the blood was eight minutes. The child was transfused with 180 c c of blood two weeks after admission, but no improvement was noted, beyond a transitory increase in the number of red blood cells.

Dr. E. S. Thompson, who examined the eyes, found in both eyes pallor of the optic nerves and depressed retinal circulation; vessels, small and pale; profuse pigment stippling over both retina with the choroidal vessels showing here and there. A low grade of retinal atrophy was present.

Clinical Course.—The child was under observation for twenty-four days after admission to the hospital, and during this entire period a distressing croupy cough was almost constantly present, which occasioned the child great discomfort. The cough was at times brassy in character, simulating somewhat the cough in adults caused by a large aortic aneurism. It was not influenced by posture. It was thought that the cough was caused by enlarged mediastinal glands.

During the period of observation, with the exception of the last few days, the child seemed moderately comfortable, except for the cough, with occasional attack of dyspnea and, at times, pain in the left side of the face.

The swelling of both cheeks became progressively more marked. The discolored areas on the face increased in extent, involving the ears and the forehead, particularly the left side (Fig. 2). Here were large irregularly shaped purplish areas with a considerable tendency to subcutaneous infiltration. Numerous new areas, averaging the size of a pea, appeared on the chest and extremities and a patch the size of a nickel was noted on the scrotum. These small patches on the body did not resemble the areas described on the face, their appearance simulated the fading stage of the eruption frequently seen in cerebrospinal fever. About two weeks after admission the left pupil dilated and remained so until the child's death.

The most striking change in the child was the rapid increase in the size of the cheeks (Fig. 2). The normal contour of the face was almost obliterated by the two symmetrical tumor masses. These masses projected beyond the tip of the nose. After a fortnight's stay in the hospital, the upper border of the masses showed small areas of softening; these softened areas did not increase in size.

Fresh subconjunctival hemorrhages occurred in both eyes (Fig. 2). Both upper eyelids became partially involved, and it was difficult, because of the increasing thickening of the upper lids, for the child to keep his eyes open. At the end of the third week, the child's condition began to grow suddenly worse, he had epistaxis, and vomited large amounts of bright red blood. It was noted about this time that many ulcerated areas in the mucous membrane of the mouth were present and that the uvula had almost entirely sloughed away. During most of the child's stay in the hospital, he had a constant but irregular temperature, generally about 102 F. A few days before death, the temperature rose to 103 F. and remained high until his death.

Death occurred twenty-four days after admission to the hospital, apparently from anemia with a terminal bronchopneumonia. Neither a necropsy nor removal of tissue sections was permitted.

DISCUSSION

Brayton [1] states that up to 1903, of seventy-five cases of this disease reported in the literature all but six were in males; since that time many cases have been reported, the majority of which were in Jews, generally males. No reported cases have been noted which resembled this case in all particulars, but almost all the conditions present in this case have been noted in a composite of other cases. In Cole and Crump's [2] case the lesions were symmetrical in distribution but began on the lower extremities instead of on the face. It is possible, that some earlier lesions on the lower extremities might have escaped notice in the case reported here. In Fordyce's [3] case epistaxis was present. He also noted that the epidermis was glossy in places as if from overdistention of the tumors. In his case there was a disposition for the tumor masses to undergo softening, apparently similar in character to the breaking down noted in this case.

All the cases described in Kaposi's [4] original monograph occurred in persons over 40 years of age and all died of the disease, although in some the condition ran a chronic course over a number of years. In the second case there was enlargement of the lymph glands, which was present in my case, but which has been mentioned by other authors as being seldom present. In Kaposi's case there was involvement of the lower lids and nose as well as of the extremities. He observed that "eventually the same sarcomatous masses occur in the mucous membrane of the trachea, the esophagus, the stomach and the intestines, particularly the large intestine." Epistaxis, brassy cough, hematemesis and bloody stools, which were present in my case, are strongly suggestive of the presence of visceral metastasis.

In Boyet's [5] case the lesions were present on all four extremities. In my case the lesions were also present on all four extremities but only during the few days prior to death was there any tendency for the lesions to spread to regions remote from the face. In many of the reported cases the lesions began on the lower extremities, gradually involved the upper extremities, then the trunk and finally the face, exactly the reverse of the course in this case.

1. Brayton, A. W.: Idiopathic Multiple Pigmented Hemorrhagic Sarcoma Cutis of Kaposi: Report of New Case and Notes of Three Preceding Ones, Indiana M. J. **21**:480, 1902.

2. Cole, H. C. and Crump, E. S.: Report of Two Cases of Idiopathic Hemorrhagic Sarcoma (Kaposi): The First Complicated With Lymphatic Leukemia, Arch. Dermat. & Syph. **3**:38 (March) 1920.

3. Fordyce, J. A.: Multiple Pigmented Sarcoma of the Skin (Kaposi), J. Cutan. Dis. **9**:1, 1891.

4. Kaposi, M.: Idiopathisches multiples Pigmentsarkom der Haut. Arch. f. Dermat. u. Syph. **4**:265, 1872.

5. Boyet: Sarcomatose idiopathique de Kaposi, J. méd. de Brux. **10**:270. 1905.

Bernhardt [6] comments on the fact that these cases are not all similar. In one of his cases, as in my case, there was involvement of the uvula and of the soft palate and some suggestion of involvement of the hard palate. He quotes Hollaender [7] who demonstrated a case before the Berlin Medical Society in which the hard palate, the tongue, the eyelids and the cheeks were the site of the lesions.

In Gilchrist and Ketron's [8] first case—the arms, face and ears gradually became involved, although the first lesion noted was on the outer side of the right leg. In their second case, as in my case, the lesion was first noted on the face. In their conclusion they state "our studies show that the lesions begin in the skin as angiomas, due to a proliferation of the interstitial connective tissue and endothelium which gradually obliterates the blood spaces, forming solid tumors. In the early stages these resemble, in some areas, young connective tissue, in other areas, sarcomata. From this beginning, then, as cutaneous angioma or later angiosarcoma, the disease spreads by metastases which first appear in the neighborhood of the primary lesion and later become widespread both in the skin and internal organs, leading, in many cases, to death."

The course of the disease as noted in my case follows closely this description, assuming, of course, that death was due, as indicated by the clinical course, to widespread metastases in the internal organs.

This disease has infrequently been noted in children. In Kolmer's case, reported by Fordyce, a girl, 8 years of age, several hundred tumors were scattered over the extremities and trunk, which underwent involution leaving behind pigmented scars. Involution of some of the tumors has been observed by a number of authors, and involution of all of the tumors in certain cases has been noted by many. In my case there was no tendency toward involution.

In other case reports the disease progressed more slowly as age advanced and seemed less severe in character.

Kaposi mentions the case of an 8 year old boy concerning whom Bilbroth had consulted him. In this child the disease began with a lesion on the leg, numerous other lesions developed, resulting in death.

Breakey [9] observed that young persons may succumb to the disease in the first or second year. He quotes Councilman, who called attention to the fact that the path of the metastases in this disease is almost always along the blood vessels.

6. Bernhardt, R.: Sarcomata idiopathica multiplicia pigmentosa cutis (Kaposi), Arch. f. Dermat. u. Syph. **49**:207, 1890.

7. Hollaender: Berl. klin. Wchnschr. **35**:107, 1898.

8. Gilchrist, T. C. and Ketron, L. W.: Report of Two Cases of Idiopathic Hemorrhagic Sarcoma (Kaposi), J. Cutan. Dis. **34**:429 (June) 1916.

9. Breakey, W. F.: Multiple Pigmented Sarcoma Cutis; Oronycosis Fungoides, Which? Tr. Mich. Med. Soc. **19**:479, 1895.

A commentary on the wide range of symptoms manifested in these cases may be gathered from an observation of Brayton's regarding his case in which the tumor masses were sensitive to pressure and their growth was attended with pain. This symptom has rarely been noted by other writers. In my case pain was present at times in the left side of the face but the tumor masses were not sensitive to pressure.

INFLUENZAL MENINGITIS

WITH REPORT OF A CASE *

ISAAC A. ABT. M.D., AND I. HARRISON TUMPEER, S.M., M.D.

CHICAGO

The literature contains many observations on meningitis caused by an organism resembling the influenza bacillus. The relationship of this organism to the so-called true influenza bacillus of Pfeiffer is still a matter of controversy. We wish to report such a case of meningitis and describe the results of the study of the organism. A variety of interesting laboratory findings were made, but the picture of the purulent meningitis remained clear cut. The bacillus was isolated from the spinal fluid, blood, throat, nose and nasopharynx. Cultures were studied and animals inoculated. The spinal fluid yielded a four plus Wassermann and reduced colloidal gold suspensions in the syphilitic zone. Morphologically typical diphtheria bacilli were found in large numbers in a nasal culture. Death occurred ten days after the onset. A necropsy was not permitted.

REPORT OF CASE

History.—The patient was referred to one of us (I. A. A.) by Dr. Mary Shutan. The child was a white male, aged 17 months, whose symptoms became manifest three days before admission to the hospital. On the first day of the illness the temperature rose to 102.4 F., but the child played and seemed to be fairly well. The following day the temperature dropped after a warm bath, but the child was very restless and vomited after nearly every ingestion of solids or liquids. There was no vomiting the next day, but occasionally afterward. Besides crying and being restless, muscular twitchings were noticed the second day, but convulsions did not occur. The right drum membrane was found bulging, and paracentesis yielded thick pus. This was repeated on both ears before admission to the hospital, and each time pus was obtained. The temperature had been subnormal for more than a day before admission, but rose subsequently. The child became very cold; rigidity was present, and the mouth had to be forced open to insert food. Strabismus was first noticed on the third day. There was no urination for periods of twelve hours on two occasions.

The birth and feeding histories were not remarkable. The patient was the third child. The parents and two other children were apparently well, and there was no history of miscarriages. The child had scarlet fever four months previously.

Physical Examination.—The patient was well nourished. He was restless and appeared to be very ill. The veins of the face were somewhat dilated. The right drum membrane was red, and there was a purulent discharge in the canal. Cultures contained staphylococci but no influenza bacilli. The left drum

was bulging and cloudy. There was an internal strabismus of the left eye; no ptosis or nystagmus. The pupils were equal and reacted to light. There was marked rigidity of the neck and extremities, and the spinal column was flexed with difficulty. The Brudzinski sign was positive, but the Kernig sign was negative. The reflexes were all very active, but no pathologic reflexes were noted. The chest and abdomen were not abnormal.

Laboratory Findings.—Blood examination on admission showed 5,120,000 red cells and 7,600 leukocytes, of which 72 per cent. were polymorphonuclears, 28 per cent. small mononuclears, 3 per cent. large mononuclears and 1 per cent. transitionals.

A morning specimen of urine was cloudy, specific gravity of 1.020; acid, and contained albumin but no sugar or acetone. There were many granular casts, a few leukocytes and occasional erythrocytes.

Throat cultures were twice reported free from diphtheria bacilli.

Spinal puncture on admission yielded 40 c.c. of turbid fluid under markedly increased pressure. A pellicle formed in five minutes. There were 3,500 cells
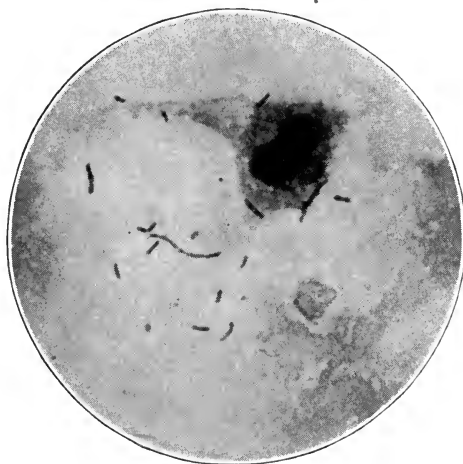
Direct smear of the spinal fluid sediment showing pleomorphism of the organism. The long thread form appears to be a series of influenza bacilli joined end to end by their cell membranes. Note the appearance of polar staining (methylene blue stain).

of which 84 per cent. were polymorphonuclears, 9 per cent. lymphocytes and 7 per cent. endothelial cells. The Noguchi, Ross-Jones and Nonne tests were markedly positive. The Wassermann test was reported $+ + + +$, and the colloidal gold test showed a reduction in the syphilitic zone.

Direct smears of the pellicle showed many polymorphonuclear cells and a gram-negative, bizarre, pleomorphic bacillus, some forms of which were long threads, others plump and tiny. Cultures yielded the same organism. Its further history is given below.

Subsequent Course.—The day following admission 15 c.c. spinal fluid was removed. This specimen was more turbid than the first, contained 10,000 cells and the same organism. At this time, ethyl hydrocuprein, 2 gr., dissolved in 8 c.c. of water was injected into the spinal canal.

On the third day since admission, the sixth of the illness, the temperature rose to 105.4 F. Despite this the child seemed bright, but was very restless. There was no Kernig sign, but the Brudzinski was slightly indicated. The

reflexes were markedly exaggerated, and the strabismus of the left eye was unchanged.

On the fifth day, the eighth of the illness, the temperature was 103.6 F. The child was comatose, and the Kernig and Brudzinski signs were now quite marked.

On the day before death, 10,000 units of diphtheria antitoxin was injected deep intramuscularly because of the finding of diphtheria bacilli in the nose the day before, despite the absence of clinical symptoms.

Attempts to obtain spinal fluid at this time failed although it was apparent that the needle was in the canal. It was concluded that the exudate had become too thick to escape through the needle inasmuch as postmortem examinations of influenzal meningitis reveal a thick, plastered exudate over the cord and brain.

In the course of the disease, at the hospital, the temperature varied between 103.8 and 105.8 F. The pulse varied from 135 to 170, and respirations from 32 to 60.

Bacteriologic Examination. — A blood culture made on the day preceding death contained influenza bacilli. Two dilutions were made in preparing the culture. One was contaminated with staphylococci. A positive result was obtained even in the dilution of 0.5 c.c. of blood to 20 c.c. of plain broth. The same pleomorphism was noted as in the spinal fluid. When subculture was made on chocolate agar, typical influenza bacilli were found, with an occasional long form.

Smears on blood agar yielded colonies of influenza bacilli from the nose, throat and posterior nasopharyngeal wall. A culture from the nose on Loeffler's medium yielded morphologically typical diphtheria bacilli.

A cultural study was made of the organism obtained from the spinal fluid. Direct smears contained slender, gram-negative bacilli of different lengths and widths. Culture on blood agar plates yielded fine, dew drop colonies with pleomorphic, gram-negative bacilli. No growth was obtained from the same fluid on plain agar or plain broth. Subcultures from the blood agar plate on chocolate agar yielded typical influenza bacilli, but a few thread forms were present. On Avery's medium the pleomorphism was more marked, and smears resembled the direct smears obtained from the original fluid. There was no growth on subculture on plain agar, plain broth, glucose broth and serum inulin water.

Animals were inoculated without producing death. A rabbit was given an intravenous injection of a twenty-four hour culture suspended in salt solution. Death did not occur although several subsequent injections were made. A white mouse was injected intraperitoneally. Instillation of a twenty-four hour growth into the nasal cavity of a guinea-pig to determine whether infection would occur by that route produced no effect.

<div style="text-align:center">DISCUSSION</div>

Cellular Content of the Spinal Fluid.—The cell count of the spinal fluid in influenzal meningitis varies, although most observers report the predominance of polymorphonuclear cells. In our case we found 3,400 and 10,000 cells, most of which were polymorphonuclear. Hill's [1] patient had fifty cells, mainly lymphocytes. Davis [2] reported four cases in which turbid fluid was present under high pressure, the polymorphonuclear cells forming from 6 to 80 per cent. of the total count. He

1. Hill: New York M. J. **107**:345, 1918.
2. Davis: Am. J. Dis. Child. **1**:249 (Feb.) 1911.

remarks on the presence of endothelial cells, which we have also found. Boland [3] reports 1,000 cells with 90 per cent. polymorphonuclear cells. The fluid in this case became so thick that it finally failed to pass through the needle. Brown [4] describes the case of a 5 months old infant who had three punctures on successive days. There were 1,600 cells with 96 per cent. polymorphonuclear cells and 3,400 and 3,600 cells the two following days, all of which were polymorphonuclears. He reports another case, an infant, 1 year old, with 6,080 cells, 73 per cent. of which were polymorphonuclears. Ross and Moore's [5] case had 86 per cent. polymorphonuclears, and Moody's [6] 11 months old patient had 256 cells, of which 230 were polymorphonuclears. Another patient, aged 8 months, had 490 cells with 90 per cent. polymorphonuclears. Bhat [7] had a 14 months old infant with 150 cells, of which 54 per cent. were polymorphonuclears and 46 per cent. lymphocytes. There were eighteen endothelial cells for 100 leukocytes. Later punctures showed more polymorphonuclear cells. Stone [8] collects two cases, Hills and his own, which had bloody fluid uniformly.

Blood Count.—Few reports in the literature mention blood counts. In our case there were 7,600 cells of which 72 per cent. were polymorphonuclears, 28 per cent. small mononuclears, 3 per cent. large mononuclears and 1 per cent. transitionals. A normal infant of 17 months averages about 40 per cent. polymorphonuclears and 60 per cent. mononuclears. There appears to be a slight leukopenia in our case although the cell count of the spinal fluid is high and the majority of the cells are polymorphonuclears. The further significance of the leukopenia in influenza is a nonspecific activity of the leukocytes, as demonstrated by Tunnicliff.[9] She states that this decreased activity continues until the patient recovers, in which case the leukocytes become normally active and increase in number. She suggests that leukopenia and diminished phagocytosis may account for the severity and frequency of secondary infections. Hill and Packard [10] state that the blood shows a moderate leukocytosis, usually under 15,000, with an increase in polymorphonuclear cells. Stone had a case in a girl, 15 years old, who had 83 per cent. polymorphonuclear cells. Moody's second patient had 12,300 leukocytes.

3. Boland: Lancet **2**:704, 1915.
4. Brown: Canad. M. A. J. **5**:1076, 1915.
5. Ross and Moore: Brit. M. J. **2**:1056, 1913.
6. Moody: J. Missouri M. A. **13**:328, 1916.
7. Bhat: Lancet **2**:384, 1917.
8. Stone: Texas State J. M. **15**:318, 1920.
9. Tunnicliff: J. A. M. A. **71**:1733 (Nov. 23) 1918.
10. Hill and Packard: Quoted in Editorial, Lancet **2**:189, 1915.

The Organism in the Spinal Fluid.—The organism found in the spinal fluid has been abundantly described. Pleomorphism in culture and smears from the meninges is its most striking feature. The descriptions are much alike. The bacilli are gram-negative and grow only on blood medium as dew drop transparent colonies. They vary in size from small, plump, coccoid organisms to long thread forms resembling leptothrix with which they have often been confused. Henry [11] states that influenza-like organisms in some cases exhibit bipolar staining which makes them resemble diplococci. He also remarks that sometimes the long forms do not appear for three or four days, while in other cases they appear early. The longer forms often predominate, and the organisms are practically always extra-cellular. This is probably an indication of diminished phagocytosis. The pleomorphism persists in subcultures on blood agar. Studying the development of pleomorphism, Brown stated that after from fifteen to twenty-four hours, minute regular bacilli appeared, among which threads were seen. On the second day, the curved forms and threads were usually increased, and the bacilli were thicker. Wollstein [12] describes the influenza bacillus as being a slender rod, varying in size, staining deeply at the poles and gram-negative. She emphasizes that the invariable and most prominent characters are, first, hemophilic property and second, pleomorphism. In one of her cases she found long forms with curved ends, often clubbed, corresponding to involution forms found in old cultures and a few characteristic small forms. In two others there were long threads but the typical small forms predominated. Bhat also speaks of long forms which were found end to end by cell membrane and Ager and Avery [13] remarked that the organism from their case exhibited polar staining and varied in size, often occurring in threadlike forms. It has been stated that the chains and convolutions are bacilli placed end to end united by continuation of the cell membrane.

The organism from Moody's second case did not grow on Loeffler's medium.

Ross and Moore isolated the organism from the fluid of the right ventricle.

Following Jordan's [14] observation on indol formation by the influenza bacillus, Rivers [15] found that eleven of twelve cases of influenzal meningitis yielded an indol reaction on the spinal fluid directly.

11. Henry: J. Path. & Bacteriol. **17:**174, 1912.
12. Wollstein: Am. J. Dis. Child. **1:**42 (Jan.) 1911.
13. Ager and Avery: Arch. Pediat. **27:**284, 1910.
14. Jordan: J. A. M. A. **72:**1542 (May 24) 1919.
15. Rivers: J. A. M. A. **75:**1495 (Nov. 27) 1920.

Its Relation to Pfeiffer's Bacillus.—The pleomorphism of the organism in this type of meningitis raises the question of its classification. Invariably, it is hemoglobinophilic. Its growth is always in the form of dew drop colonies only produced by the influenza bacillus described by Pfeiffer. It is always gram-negative. However, animal inoculations give varying results, and its morphology is somewhat perplexing. There are many who believe that the organism producing meningitis is a bacillus quite distinct from Pfeiffer's bacillus. They insist that this is a pseudo-influenza or an influenzoid organism. Cohen [16] is the chief proponent of this separate organism theory. He states that a septicemic type of influenza bacillus exists which causes meningitis, inasmuch as experimental septicemia cannot be produced, except in those with influenzal meningitis. He concurs with Pfeiffer's original view that the organism does not occur in the blood, but that the meningeal type produces a septicemia in rabbits with serous lesions, as in the human. He has found that vaccination may be carried out against the organism, but the serum of vaccinated animals is neither curative nor preventive, and phagocytic and agglutinative reactions do not distinguish this organism sufficiently from Pfeiffer's bacillus. The differences are summed up in this way by Henry. The organism from meningitis shows bacillary and filamentous forms in culture more readily than does Pfeiffer's organism. It is more readily recovered from heart's blood and tissues than the organism from influenza. It tends to kill laboratory animals by septicemia rather than by toxemia, and fatal results occur with much greater regularity than is the case with Pfeiffer's bacillus.

On the other hand, Wollstein believes that it may be considered as conclusively established that a pseudo-influenza bacillus producing pathologic conditions in human beings as distinct from the true influenza bacillus does not exist. She suggests that the frequent finding of the influenza bacillus in endocarditis, purulent arthritis, empyema, appendicitis, peritonitis, meningitis, otitis, as well as its frequent occurrence in the bronchial and nasopharyngeal secretions in cases of clinical influenza indicates that that organism, like the pneumococcus, is capable of causing inflammations of the serous membranes anywhere in the body. Along these lines Rivers offers the suggestion that the influenza [17] bacillus may be a group of organisms like the streptococcus, which has been divided into hemolytic and nonhemolytic strains and further subdivided by cultural characteristics and serologic tests. He exacts ten requirements for the true influenza bacillus. These tests are hemophilic quality, colony formation, hemolytic test, reaction to Gram's

16. Cohen: Ann. de l'Inst. Past. **23**:273, 1909.
17. Rivers: Bull. Johns Hopkins Hosp. **31**:50, 1920.

stain, morphology, motility, indol formation, found by Jordan to occur in ten of thirteen strains, reduction of nitrates to nitrites, amylase formation and reaction in blood, broth and milk. Further evidence that the meningeal organism is the true influenza bacillus is offered by Slawyk,[18] who isolated a bacillus from the blood and spinal fluid in meningitis which Pfeiffer agreed was the influenza bacillus, and by Thursfield,[19] who found the organism in the blood without meningitis. Flexner [20] interprets the situation by expressing that nearly all cases of influenzal meningitis are examples of bacteremia, since the bacilli are frequently cultivated in large numbers from the blood during life or at necropsy.

To compromise the two views, Henry states that there is a group of hemoglobinophilic organisms causing meningitis whose members range from the influenza bacillus of Pfeiffer which, when it kills, does so by toxemia, to Cohen's organism of very high virulence which kills laboratory animals regularly by septicemia. Ross and Moore state it is impossible to dogmatize whether the organism isolated from sporadic cases of meningitis is identical with the organism in the respiratory tract in influenza. It is sufficient to say that there is a group of cases showing pyemic characters in which meningitis is a common occurrence and in which the only organism present is a hemophilic bacillus having the characteristics of the influenza bacillus. After all these reports and opinions, is it not possible that the influenza bacillus is subject to involutions? The conditions of growth in the spinal canal are somewhat comparable to the conditions in a fluid medium such as Avery's medium. We found that the typical influenza bacilli which were grown by subculture of the pleomorphic bacillus from the spinal fluid on the solid medium of chocolate agar reverted to pleomorphism when grown in Avery's medium.

Animal Inoculation.—The organism in our case was not pathogenic for guinea-pigs, rabbits or mice, despite repeated injection. There are reports of other organisms which illustrate the low pathogenicity we found. Henry injected three rabbits intravenously, intraperitoneally and subcutaneously, respectively, with no illness resulting and no findings when the animals were killed. Ager and Avery failed to produce infection in a guinea-pig inoculated with the organism from their patients, but a rabbit previously bled 15 c.c. died in forty-eight hours. Torrey's [21] organism was of low pathogenicity tested by rabbits. Ritchie's [22] observations differ to this extent. The real influenza bacillus

18. Slawyk: Ztschr. f. Hyg. **32**:443, 1899.
19. Thursfield: Quoted by Rivers, Reference 17.
20. Flexner: J. A. M. A. **57**:16 (July 3) 1911.
21. Torrey: Am. J. M. Sc. **152**:403, 1915.
22. Ritchie: J. Path. & Bacteriol. **14**:615, 1910.

is at first innocuous to guinea-pigs but after subculture for five months it gives a septicemia in guinea-pigs by intraperitoneal injection.

Many observers obtain positive results by animal inoculation. The second generation of the organism from Hill's case inoculated intra-peritoneally into a white mouse caused death in less than twenty-four hours. Intravenous injection into a 900 gm. rabbit was followed by death in thirty-six hours, and the organism was recovered from the heart's blood. Wollstein's work in 1911 demonstrated that mice were highly susceptible to small injections intraperitoneally whether the cerebrospinal fluid or pure cultures of the organism were used. Animal passage through mice did not appreciably increase the virulence, although only one half the dose was required to kill after passage.

Guinea-pigs died in from twelve to twenty-six hours after injection of from one-half to whole cultures. Rarely was phagocytosis found, although there were polymorphonuclear cells in the peritoneum. Some-times, the animals lived for three or four days.

Rabbits injected with twenty-four hour cultures died in from fifteen to thirty-six hours, and the bacilli were recovered from the mucosal surface of the upper nasal cavities.

Monkeys injected subdurally by spinal puncture yielded symptoms in from six to twelve hours.

Wollstein found that out of a large number of strains, four were found to be virulent for rabbits. Three of these were obtained from influenzal meningitis spinal fluid. Many necropsies were examined for bacilli from the blood without results. She states that the bacilli are more frequently isolated from the blood postmortem in the cases of meningitis. All strains were found virulent for small animals. In general, the high virulence for human beings ran parallel with the effects on rabbits and monkeys.

Albert and Kelman [23] find that the bacilli are usually destroyed rapidly after their introduction into the body, but following intraperi-toneal injections, the organism may appear in the blood. They also state that the bacillus produces a toxin which is fatal to mice, guinea-pigs and rabbits almost as soon as broth cultures. Death occurs in from one and one-half hours to thirty days after injection. They suggest that death occurring after four days may be caused by second-ary invading organisms. It is their experience that guinea-pigs are more uniformly susceptible than rabbits or mice, and rabbits show a greater individual variation in susceptibility. On the basis of their work, they conclude that the influenza bacillus is distinctly pathogenic to mice, guinea-pigs and rabbits, but that this quality is apparently limited to certain cultures or strains of the organism.

23. Albert and Kelman: J. Infect. Dis. **25**:433, 1919.

PATHOGENESIS

The influenza bacillus behaves like the pneumococcus. It has been found in the mouth in 43 per cent. of persons [24] examined. Considering the upper respiratory tract as the most frequent portal of entry, Wollstein explains the localization of the organism in the middle ear, bronchi and lungs. In Brown's case of a 5 months' old infant there was double otitis media with preceding bronchitis, in which the influenza bacillus was found in pure culture. The blood, nasopharyngeal and postmortem culture of brain, heart's blood, lung and mastoid all yielded the organism. This well illustrates the belief of Wollstein that the influenza bacillus acts like the pneumococcus and is equally as capable of producing inflammations of the serous membranes anywhere in the body.

To determine the rôle of the upper respiratory tract in the etiology of influenzal infections Bloomfield [25] introduced the organism into the upper respiratory passages. Several strains so introduced disappeared in from one to three days. No carrier states were produced, and no local or general pathologic processes resulted from the inoculation. Bacilli isolated more than twenty-four hours after introduction were shown to be different strains, and they were not viable after suspension in saliva for twenty-four hours at 37 degrees C.

The middle ear undoubtedly plays an important rôle in the development of influenzal meningitis in children. Ritchie quotes Kossel as finding in 108 postmortem examinations in children under 1 year of age, eighty-five cases of otitis media, over half of which were of influenzal meningitis. Hartman and Honel [26] have found 90 per cent. of cases of otitis media in infants of influenzal origin. Our case may have been one of influenzal otitis media originally although late cultures showed staphylococci which may have been secondary invaders. Suppuration of the frontal and maxillary sinuses was the source of infection in Torrey's first case. Henry states that infection may come directly through the carious bone or by blood vessels running through the remains of the petrosal squamosal suture from the antrum to the middle fossa without direct extension or caries. The nasopharynx, he suggests, may be the portal through which the bacilli are conveyed by the nasal lymphatics to the anterior fossa of the skull, through the cribriform plate of the ethmoid.

Opinion seems to favor a bacteriemia as the mechanism in the production of meningitis, although this cannot always be demonstrated. Inoculation of the bacilli intravenously in rabbits has resulted in positive blood culture postmortem. Following intraperitoneal injection they

24. Pritchell and Stillman: J. Exper. M. **29**:259, 1919.
25. Bloomfield: Bull. Johns Hopkins Hosp. **31**:85, 1920.
26. Hartman and Honel: Quoted by Henry, Reference 11.

may appear in the blood, probably depending on the virulence of the organism and the lowered resistance on the part of the body.[23] After subdural inoculation, they may be recovered from the upper nasal mucosa, suggesting that they are excreted at this point.[13] Since they also reach the blood, they may be secreted from the blood and not directly through the meninges. After intravenous injection of influenza bacilli into rabbits they are found in the secretions of the mucosa. They are excreted by the kidneys in rabbits and guinea-pigs, and pure cultures may be obtained from the surface of the cord and brain in rabbits and guinea-pigs inoculated intravenously or intraperitoneally, although no lesions or inflammations of the meninges are found. From this experimental evidence, Wollstein believes that the bacilli may be present in the spinal fluid without causing meningitis and permitting a clear fluid.

In furtherance of the theory of bacteremic pathogenesis of influenzal meningitis, Henry thinks that the occurrence of bronchopneumonia, pleurisy and pericardial inflammations, complicated with meningitis, allows the assumption that the bacilli are carried to the meninges by the blood stream or pass to the cervical meninges by the thoracic lymphatics, as in some cases of tuberculous meningitis. It will be remembered that Flexner stated that nearly all cases of influenzal meningitis are examples of bacteriemia, as demonstrated by the frequent positive blood findings during life or at necropsy. Davis states that the meningeal infection is probably hematogenous in origin, even though the heart's blood cultures after death may be negative. Difficulties encountered in making blood cultures in young children during life are responsible for the absence of data on this point, but we can say that in the majority of the fatal cases of influenzal meningitis a general blood infection occurs whether this invasion is primary or secondary.

PROGNOSIS

More cases of influenzal meningitis occur in infants and young children than in adults, and the process is more severe in children. Stone collected 105 cases, with a mortality of 91.4 per cent., nine patients recovering.

TREATMENT

To reduce the high mortality many agencies have been tried. From the medicinal standpoint, hexamethylenetetramin, in 10 grains doses, at four hour intervals was followed by improvement in one case reported by Ross and Moore although the final outcome is not reported.

The diminished phagocytosis in influenzal infections suggests that favorable results may be obtained by measures aimed to increase leukocytic activity. Practically no phagocytosis occurs, as is evidenced by

the extracellular arrangement of the organism in the spinal fluid. In fact, there seems to be evidence for Torrey's contention that protective substances may pass out into the spinal fluid following spinal puncture due to lowered pressure and consequent increased outpouring into the cerebrospinal space. Following lumbar puncture, there is increased phagocytosis and decrease in the organism. In one of Torrey's cases, the organism became intracellular at the second puncture. The good effect following tapping, he states, may also be due to relief of high pressure, improved blood supply, and removal of toxins.

Spinal lavage in Ross and Moore's case resulted in a less involved spinal cord than brain.

Regarding specific therapy, Cohen states that animals may be vaccinated against the organism, but that the serum of vaccinated animals is neither curative nor preventive. Tunnicliff suggests that convalescent serum or immune horse serum may promote leukocytosis and increase antibody content of the serum. In this connection Johnson [27] reports the case of a 3 year old boy who recovered following the injection of convalescent serum intraspinally and subcutaneously. It is to be expected that normal serum may increase phagocytosis and improve the condition.

CONCLUSIONS

1. Influenzal meningitis is accompanied by a widespread distribution of the influenza bacillus in the upper respiratory tract.

2. The organism is easily cultivated from the spinal fluid and in many cases from the blood.

3. The organism from the spinal fluid is usually pleomorphic, showing many long thread forms.

4. It seems plausible that the pleomorphism is but a minor variation from the so-called typical influenza bacillus, and that this may be due to the peculiar conditions of its habitat.

5. Spinal fluid usually contains a large number of polymorphonuclear cells which show no tendency to phagocytosis.

6. The blood count does not give the typical leukopenia of respiratory influenza.

7. Animals show a variable response to injections of the organism, although the bacillus is usually pathogenic for laboratory animals.

8. Prognosis of influenzal meningitis is very grave.

9. The most rational treatment at the present time is the administration of convalescent or normal serum and frequent removal of spinal fluid. The serum contains antibodies and promotes phagocytosis, and spinal puncture removes fluid and increases phagocytosis.

---

27. Johnson: Arch. Pediat. **36**:82, 1919.

A PRELIMINARY REPORT OF THE STUDY OF BREAST FEEDING IN MINNEAPOLIS *

JULIUS PARKER SEDGWICK, B.S., M.D.

Professor and Chief of the Department of Pediatrics, School of Medicine, University of Minnesota

MINNEAPOLIS

Most of the members of this organization have heard me in season and out of season, talking about breast feeding, and the study we have been making of it at the University of Minnesota. Although the statistics will not be ready until September, enough data have come so that we have records which indicate what we have learned and accomplished. I have had so many inquiries in regard to our technic, that I am taking this opportunity to explain the essential parts to those who are interested.

The investigation of breast feeding in Minneapolis was planned to study the wider applicability of certain principles of breast feeding which we have been using at the University of Minnesota and in private work. We wished to see whether these principles are applicable to a wider field, and to all strata of society. We wished to make a statistical study to observe the effect, if any, on infant mortality. Dr. Rood Taylor made a study of the records of our New-born Clinic at the University recently and he found that in one thousand consecutive cases in which the mother and the baby left the hospital together each child was at the breast. This disposes of the importance of the bogey, agalactia. The idea that the mothers often have no milk for their new-born babies was not given much consideration in this study. The technic of the maintenance and reestablishment of breast feeding is that which I described in my chairman's address in New York in 1917 [1] and I shall mention simply the essentials here.

The demand which is made on the breast is by far the most important factor in the maintenance of the breast milk supply. Repeated, regular and complete evacuation of the breasts by a vigorous baby, is, of course, the natural and best method. When this natural stimulus is not obtained or when the demand on the breast is insufficient for any reason, the supply of breast milk dwindles gradually until the breast does not support the baby. In these cases artificial aid is

---

necessary. In an interesting paper published in 1913, Zlocisti showed that this can be accomplished by putting the father at the breast, and stimulating the lactation systematically. This, however, is open to many esthetic and social objections. We have found that in most cases, using the principle of stimulation but by milking the breast, we are able to accomplish a similar or even better result. A cross section of the breast shows that the milk sinuses are largely just back of or in the area under the colored areola. The gland proper is farther back. We apply the same principles that the milkmaid applies. She does not stroke the cow's udder. She grasps the teats only. We do not massage or stroke the breasts over the glandular tissue as this often causes injury. We grasp the breast just back of the colored areola, press the forefinger and thumb together, thus closing off the sinuses. Then, using a milking motion, push forward then outward, thus emptying the ducts and sinuses to the nipple itself. This should be done gently and should not be painful. No trauma should be done the nipple and the gland tissue of the breast itself is not injured.

Let us consider the premature baby first. Many a premature baby has been deprived of its mother's breast milk unnecessarily. The milk of the mother of the premature baby dries up, not because of the baby being born prematurely, but because the premature baby cannot make the proper demand on the breast. We make the practice of milking the mothers breasts as described above, and giving the milk to the premature baby, usually by means of a tube. In our experience these mothers of premature babies furnish milk just as well as mothers of full time babies, and in case after case we have found that these mothers who are milking their breasts, and not laying the baby on the breast on account of the weakness of the baby, have just as good a milk supply, and often are able to furnish milk for their own babies and for another baby besides. When we have intelligent mothers who cooperate well we do not at all feel that the breast feeding of the premature baby is difficult.

It may take a little more time but the mothers are almost always sympathetic and willing to aid in this work and do not complain of the extra time involved. Most of our premature babies are fed with a tube for a month or two before they are laid at the breast at all. It is certainly much less trouble than wet nursing.

It is not only in cases of prematurity that this method is of value for keeping the breast milk up. When a baby is weak from any cause, or ill, so as not to be with the mother, or even when the mother is required to be away for a period, as in one case for two weeks, this method will keep the supply up.

When the trouble is with the breast or the nipple itself, this

method may be used to advantage. In one case a mother had failed to nurse two children because of a badly inverted nipple on one side. With the third lactation she was shown how to express the milk and encouraged in carrying out this procedure over a long period. At the end of nine months, she was nursing the baby at one breast fully and on the other she had expressed the milk at every feeding; five times in every twenty-four hours during the whole nine months period. When she appeared for the weaning of the baby, at the end of nine months she was getting more milk from the breast on which she could not lay the baby, and from which she had expressed the milk regularly, thus furnishing the stimulation artificially, than she was getting from the breast on which the baby was being laid. In cases in which the nipple is sore or where there is a fissure, this method can be used to let the nipple have the proper rest, and at the same time the breast milk is not lost for want of stimulation. Expression can be used without any injury to the nipple itself. It would be a mistake to leave the impression that we depend wholly on expression in this study of breast feeding. Every other method of encouraging and instructing the mothers in breast feeding is applied also. Expression is reserved largely for the more difficult cases. However, I wish to stress the demand made on the breast and the expression as the important means, rather than the very common giving of enormous quantities of fluid. We know enough now about the physiology of the breast, if we could apply it, to get at least 90 or 95 per cent. of the babies nursed at the breast.

In organizing the bureau for carrying on this study, we began with the medical men. We wrote to every physician in the city announcing the formation of the bureau, we invited them to meet at the University, and explained the purpose; we sent representatives to talk with them and explain all details. We made it quite plain that no physician in active practice would be employed in connection with the work. I was fortunate in that I was confining my private work to consultation and referred work. Each physician was asked for criticisms. A card index of the physicians was maintained on which any special desire of the physicians was recorded. In most cases the physicians wished that we go directly into the cases, but report to them afterward. Some wished, however, to have us report to them before going in. Some wished all our statements and directions to come through them personally. We respected all these wishes. After we had been in operation some time, we sent a representative to all the physicians again to ask whether we were embarrassing them in any way, and asked for suggestions to prevent such embarrassment. The Minneapolis Health Department cooperated in every way possible; not

only passively but actively. The Infant Welfare Society took up the work of getting information for us from the families with whom they were working. Prominent citizens and the daily papers participated and aided in many ways.

The Breast Feeding Investigation Bureau of the Department of Pediatrics of the University of Minnesota was the name under which the work was carried on. The graduate school of the University appropriated $1,000 for the study.   The war chest appropriated $3,000. From private individuals and other sources, about $1,500 more was paid, thus making the total amount between five and six thousand dollars for the year's study.

The mother of practically every baby born in Minneapolis during the year was followed for nine months. The birth reports were sent in from the health department every day, and the first information concerning the breast feeding was obtained by telephone or personal call. If things were going well literature was sent each month. If the return cards were not sent back, the case was followed up by telephone or personal call. If there was any trouble with the breast feeding, the bureau was thus informed and the doctor was consulted, a nurse sent out to instruct the mother when necessary, even daily. The literature was as follows:

1. Is your baby being breast fed?...
2. If not, when and why did you stop?....................................
3. How many other children have you had?................................
4. Give years of births: 1.......... 2..........:.. 3.......... 4.........
5. How many are living?..
6. If you have lost any, at what ages and from what cause?................
   ....
7. How long was each child at the breast only? (If but a few days or short time, state as nearly as possible the number of days.)
   1............ 2............ 3............ 4............
8. When was the breast stopped in each case?
   (1)........mos. (2)........mos. (3)........mos. (4)........mos.
9. Give reason for stopping breast feeding in each case if before the ninth month.
   1............ 2.......... 3............ 4............
10. If bottle was given with the breast, when was it begun and was it in addition to each breast feeding or in place of certain breast feedings.
   1............ 2............ 3............ 4............
        I can be reached by Phone No....................................

POST CARD

Dear Madam :

Summer will soon be here. It is especially important now for your baby to be kept upon the breast. There is much more danger for the bottle-fed baby when the weather is hot.

We wish to make sure again that you have no difficulty with the breast feeding which can be prevented.

We are, therefore, taking the liberty of sending you another card, asking you to answer the following questions and return it to us.

Thank you.

For THE BREAST FEEDING INVESTIGATION BUREAU.

....
(1) Is your baby still breast-fed?..
(2) How often do you feed it?..
(3) Does it receive the breast only?.......................................
(4) Are you having any difficulty nursing the baby?.......................
....
(5) If so, what?..
(6) If not breast-fed, when and why did you stop? (State how long the baby
    was breast-fed.) ....
....

POST CARD

(1) Is your baby still breast-fed?..
(2) How often do you feed it?..
(3) Does it receive the breast only?.......................................
(4) Are you having any difficulty nursing the baby?.......................
....
(5) If so, what?..
(6) If not breast-fed, when and why did you stop? (State how long the baby
    was breast-fed.) ....
....
....
....
Have you or the baby had influenza?.......................................
Have you a telephone?...

A report was obtained concerning each child every month.

Such work is usually done in clinics and hospitals, but we reached everybody, rich and poor. We were told, and we also feared, that we would have great difficulty in the private families where the physicians were in charge. This, however, we found not to be true. In almost every case the physician was sympathetic and aided us. When our agents found that there was difficulty with breast feeding we often asked the physician to give us his support, which he almost always did. Many of our workers have reported that they had even less trouble with those who were educated and had means to pay for services of their own physicians and nurses.

Jan. 1, 1920, this work was turned over to the Infant Welfare Society of Minneapolis, thus making it permanent. The final report cannot be given out until nine months after January 1, as babies born in December, 1919, will not be nine months old until September, 1920. The Infant Welfare Society is giving us reports to complete our records.

I would, however, call your attention to the beginning of the report where the total results of the investigation for January, February, March, April and May are listed. The results by months run from 96 per cent. at the end of the second month to 72 per cent. at the end of the ninth month.

TABLE 1.—Total Result of Investigation of Breast Feeding of the January, February, March, April and May Babies Born in Minneapolis During 1919

	Breast Fed		Percentage on Arti- ficial Food
	Number	Per Cent.	
Of the 2,022 babies still under observation at the end of the ninth month..................................	1,472	72+	27+
Of the 2,113 babies still under observation at the end of the eighth month............................ ...	1,631	77+	22+
Of the 2,240 babies still under observation at the end of the seventh month................................	1,810	80+	19+
Of the 2,355 babies still under observation at the end of the sixth month.................................	1,992	84+	15+
Of the 2,412 babies still under observation at the end of the fifth month..................................	2,090	86+	13+
Of the 2,505 babies still under observation at the end of the fourth month................................	2,250	89+	10+
Of the 2,674 babies still under observation at the end of the third month.................................	2,492	93+	6+
Of the 2,847 babies still under observation at the end of the second month...............................	2,761	96+	3+

TABLE 2.—January, 1919, Cases

Six hundred and thirty-six babies were born in Minneapolis during January, 1919. Of these, at the end of each month listed, the data are shown.

	Jan. 31, 1919	Feb. 28, 1919	March 31, 1919	April 30, 1919	May 31, 1919	June 30, 1919	July 31, 1919	Aug. 31, 1919	Sept. 30, 1919
Breast fed........................	516	486	427	590	345	301	224	146	88
Breast fed complemental*........	33	41	67	66	75	94	138	198	242
Total breast fed†.............	549	527	494	656	420	395	362	344	330
Artificially fed.................	...	8	24	39	56	80	70	75	85
Total under observation‡........	549	535	518	495	476	455	432	419	415
Artificially fed from birth........	13	13	13	13	13	13	13	13	13
Baby died........................	18	21	25	27	28	29	29	31	31
Mother died......................	3	3	3	3	3	3	3	3	3
Refused to give information.....	0	3	3	5	5	6	7	7	7
Moved out of town..............	2	6	13	23	31	40	46	48	49
Cannot be traced................	11	15	21	30	40	50	66	75	78
Out of town cases...............	40	40	40	40	40	40	40	40	40
	636	636	636	636	636	636	636	636	636

RESULT

	Breast Fed		Percentage on Arti- ficial Food
	Number	Per Cent.	
Of the 415 January babies still under observation Sept. 30, 1919	330	79+	20+
Of the 419 January babies still under observation Aug. 31, 1919	344	82+	17+
Of the 432 January babies still under observation July 31, 1919	362	83+	16+
Of the 455 January babies still under observation June 30, 1919	395	86+	13+
Of the 476 January babies still under observation May 31, 1919	420	88+	10+
Of the 495 January babies still under observation April 30, 1919	456	92+	7+
Of the 518 January babies still under observation March 31, 1919	494	95+	4+
Of the 535 January babies still under observation Feb. 28, 1919	527	98+	1+

* By "complemental" is meant breast fed with an addition of some artificial mixture after the breast feeding.

† Sixty-seven mothers of January babies were taught expression of milk from the breasts in order to stimulate the breasts and thereby increase the milk supply.

‡ Jan. 31, 1919, we had 549 of the babies born in January under observation. Sept. 30, 1919, we had 415 of these babies still under observation, 134 of the 549 babies under observation on Jan. 31, 1919, having been dropped for the following reasons: baby died, 13 cases; refused to give information, 7 cases; moved out of town, 47 cases; cannot be traced, 67 cases.

TABLE 3.—February, 1919, Cases

Six hundred and twenty-one babies were born in Minneapolis during February, 1919. Of these, at the end of each month listed, the data are presented.

	Feb. 28, 1919	March 31, 1919	April 30, 1919	May 31, 1919	June 30, 1919	July 31, 1919	Aug. 31, 1919	Sept. 30, 1919	Oct. 31, 1919
Breast fed....................	520	493	418	362	326	260	188	116	77
Breast fed complemental........	31	46	61	63	78	126	168	215	224
Total breast fed*............	551	539	479	425	404	386	356	331	301
Artificially fed..............	...	4	21	38	44	57	77	88	91
Total under observation†........	551	543	500	463	448	443	433	419	392
Artificially fed from birth........	11	11	11	11	11	11	11	11	11
Baby died........................	20	23	23	24	25	26	28	28	28
Mother died......................	1	1	3	3	3	3	3	3	3
Refused to give information.....	0	0	1	1	1	2	2	2	2
Moved out of town..............	0	3	19	39	39	40	41	45	54
Cannot be traced................	4	6	30	46	60	62	69	79	97
Out of town cases..............	34	34	24	34	34	34	34	34	34
	621	621	621	621	621	621	621	621	621

RESULT

	Breast Fed		Percentage on Artificial Food
	Number	Per Cent.	
Of the 392 February babies still under observation Oct. 31, 1919	301	77+	22+
Of the 419 February babies still under observation Sept. 30, 1919	331	78+	21+
Of the 433 February babies still under observation Aug. 31, 1919	356	82+	17+
Of the 443 February babies still under observation July 31, 1919	386	87+	12+
Of the 448 February babies still under observation June 30, 1919	404	90+	9+
Of the 463 February babies still under observation May 31, 1919	425	91+	7+
Of the 500 February babies still under observation April 30, 1919....................................	479	95+	4+
Of the 543 February babies still under observation March 31, 1919	539	99+	¼+

* Fifty-four mothers of February babies were taught expression of milk from the breasts in order to stimulate the breasts and thereby increase the milk supply.
† Feb. 28, 1919, 551 of the babies born in February were under observation. Oct. 31, 1919, 392 of these babies were still under observation, 159 of the 551 babies under observation Feb. 28, 1919, having been dropped for the following reasons: baby died, 8 cases; mother died, 2 cases; refused to give information, 2 cases; moved out of town, 54 cases; cannot be traced, 93 cases.

The cold figures are lifeless but, of course, necessary. I have often thought of it in comparison with our judgment of certain therapeutic procedures. The statistics of the effect of diphtheria antitoxin are of interest and, of course, are also necessary, but each of us has seen the brilliant effect of the administration of the serum in the individual cases which appeals to us more. I remember the enthusiasm of my father, who practiced medicine during the time of the introduction of antitoxin. In like manner our workers became enthused over the fine results in the individual cases. We find that many of them

who could not well afford it were willing to do this work for less pay because of the remarkable results that they saw before them. One of the members of this society once heard me discussing this subject. He evinced some interest and some mental reserve. Later he came out to see us and I sent him out into the field with a nurse, keeping away myself. He saw two cases and ceased to be skeptical about maintenance of breast feeding and was wholly convinced and enthusiastic.

We wish now to supplement this study with one of rural conditions in the state.

Through the members of our staff who are sent out on our rural clinics, we get reports from certain districts in which rickets is very

TABLE 4.—March, 1919, Cases

Seven hundred and ninety-nine babies born in Minneapolis during March, 1919. Of these, at the end of each month listed, the data are presented.

	March 31, 1919	April 30, 1919	May 31, 1919	June 30, 1919	July 31, 1919	Aug. 31, 1919	Sept. 30, 1919	Oct. 31, 1919	Nov. 30, 1919
Breast fed..........................	615	541	470	429	377	339	234	130	62
Breast fed complemental.........	30	52	78	74	88	115	181	261	273
Total breast fed*.............	645	593	548	503	465	454	415	391	335
Artificially fed...............	...	41	58	74	87	96	102	119	132
Total under observation†.......	645	634	606	577	552	550	517	510	467
Artificially fed from birth........	25	25	25	25	25	25	25	25	25
Baby died......................	20	29	30	32	32	32	35	35	35
Mother died....................	5	5	5	5	5	5	5	5	5
Refused to give information.....	1	1	1	1	1	1	1	1	1
Moved out of town..............	15	16	25	39	49	50	62	67	90
Cannot be traced................	25	26	44	57	72	73	91	93	113
Out of town cases...............	63	63	63	63	63	63	63	63	63
	799	799	799	799	799	799	799	799	799

RESULT

	Breast Fed		Percentage on Artificial Food
	Number	Per Cent.	
Of the 467 March babies still under observation November 30, 1919	335	71+	28+
Of the 510 March babies still under observation Oct. 31, 1919	391	76+	23+
Of the 517 March babies still under observation Sept. 30, 1919	415	80+	19+
Of the 550 March babies still under observation Aug. 31, 1919	454	82+	17+
Of the 552 March babies still under observation July 31, 1919	465	84+	15+
Of the 577 March babies still under observation June 30, 1919	503	87+	12+
Of the 606 March babies still under observation May 31, 1919	548	90+	9+
Of the 643 March babies still under observation April 30, 1919	593	93+	6+

* Eighty-three mothers of March babies were given special attention and taught expression of milk from the breasts in order to stimulate the breasts and thereby increase the milk supply.
† March 31, 1919, 645 of the babies born in March were under observation. Nov. 30, 1919, 467 of these babies still were under observation, 178 of the 645 babies under observation March 31, 1919, having been dropped for the following reasons: baby died, 15 cases; moved out of town, 75 cases; cannot be traced, 88 cases.

common. In these neighborhoods infants are weaned for insufficient reasons. Fortunately, most of the children in the territory covered by our rural clinics, are breast fed. The study of breast feeding in smaller towns and rural districts should be very interesting, and should be made through the physicians as in Minneapolis. The conditions in certain other cities of large and smaller size and the same size over the country should be determined. Minneapolis has a low infant mortality for a city of its size. However, for the first year of the application of this work, the mortality dropped definitely. This may be entirely coincident, but I do not believe that it is.

TABLE 5.—April, 1919, Cases

Seven hundred and nineteen babies born in Minneapolis during April, 1919. Of these, at the end of each month listed, the data are given.

	April 30, 1919	May 31, 1919	June 30, 1919	July 31, 1919	Aug. 31, 1919	Sept. 30, 1919	Oct. 31, 1919	Nov. 30, 1919	Dec. 31, 1919
Breast fed......................	599	573	486	436	386	312	185	93	35
Breast fed complemental........	17	27	56	70	93	134	225	221	224
Total breast fed*............	616	600	542	506	479	446	410	314	259
Artificially fed..............	...	8	22	30	47	60	74	89	128
Total under observation†........	616	608	564	536	526	506	484	403	387
Artificially fed from birth........	7	7	7	7	7	7	7	7	7
Baby died.....................	19	25	25	26	27	27	28	28	29
Mother died...................	1	1	2	2	2	2	2	2	2
Refused to give information.....	0	0	0	0	0	0	0	0	0
Moved out of town..............	8	9	35	48	53	62	67	70	71
Cannot be traced...............	15	16	33	47	51	62	77	155	169
Out of town cases..............	53	53	53	53	53	53	53	53	53
	719	719	719	719	719	719	719	719	719

RESULT

	Breast Fed		Percentage on Artificial Food
	Number	Per Cent.	
Of the 387 April babies still under observation Dec. 31, 1919	259	66+	33+
Of the 403 April babies still under observation Nov. 30, 1919	314	77+	22+
Of the 484 April babies still under observation Oct. 31, 1919	410	84+	15+
Of the 506 April babies still under observation Sept. 30, 1919	446	88+	11+
Of the 526 April babies still under observation Aug. 31, 1919	479	91+	8+
Of the 536 April babies still under observation July 31, 1919	506	94+	5+
Of the 564 April babies still under observation June 30, 1919	542	96+	3+
Of the 608 April babies still under observation May 31, 1919	600	98+	1+

* Sixty mothers of April babies were taught expression of milk from the breast in order to stimulate the breasts and thereby increase the milk supply.

† April 30, 1919, we had 616 of the babies born in April under observation. Dec. 31, 1919, we had 387 of these babies still under observation, 229 of the 616 babies under observation April 30, 1919, having been dropped for the following reasons: baby died, 10 cases; mother died, 2 cases; moved out of town, 63 cases; cannot be traced, 154 cases.

TABLE 6.—MAY, 1919, CASES

Six hundred and fifty-seven babies born in Minneapolis during May, 1919. Of these, at the end of each month listed, the data are shown.

	May 31, 1919	June 30, 1919	July 31, 1919	Aug. 31, 1919	Sept. 30, 1919	Oct. 31, 1919	Nov. 30, 1919	Dec. 31, 1919	Jan. 31, 1920
Breast fed........................	506	446	363	301	266	221	164	87	66
Breast fed complemental.........	32	56	66	59	56	90	103	164	181
Total breast fed*............	538	502	429	360	322	311	267	251	247
Artificially fed...............	...	16	54	74	88	90	107	111	114
Total under observation†........	538	518	483	434	410	401	374	362	361
Artificially fed from birth........	11	11	11	11	11	11	11	11	11
Baby died........................	17	22	22	24	24	25	26	26	26
Mother died......................	2	2	2	2	2	2	2	2	2
Refused to give information.....	0	0	0	0	0	0	0	0	0
Moved out of town..............	7	9	19	32	53	56	56	59	59
Cannot be traced................	30	43	68	102	105	110	136	145	146
Out of town cases...............	52	52	52	52	52	52	52	52	52
	657	657	657	657	657	657	657	657	657

RESULT

	Breast Fed		Percentage on Artificial Food
	Number	Per Cent.	
Of the 361 May babies still under observation Jan. 31, 1920	247	68+	31+
Of the 362 May babies still under observation Dec. 31, 1919	251	69+	30+
Of the 374 May babies still under observation Nov. 30, 1919	267	71+	28+
Of the 401 May babies still under observation Oct. 31, 1919	311	77+	22+
Of the 410 May babies still under observation Sept. 30, 1919	322	78+	21+
Of the 484 May babies still under observation Aug. 31, 1919	360	82+	17+
Of the 483 May babies still under observation July 31, 1919	429	88+	11+
Of the 518 May babies still under observation June 30, 1919	502	96+	3+

* Forty-five mothers of May babies were taught expression of milk from the breasts in order to stimulate the breasts and thereby increase the milk supply.

† May 31, 1919, 538 of the babies born in May were under observation. Jan. 31, 1920, 361 of these babies still were under observation, 177 of the 538 babies under observation May 31, 1919, having been dropped for the following reasons: baby died, 9 cases; mother died, 52 cases; cannot be traced, 116 cases.

TOXIC SYMPTOMS IN INFANTS AND CHILDREN WITH GASTRO-INTESTINAL MANIFESTATIONS. *

HERMAN SCHWARZ, M.D., AND JEROME L. KOHN, M.D.
NEW YORK

Severe toxic symptoms have long been described in infants who are suffering from various intestinal conditions, but the peculiar group of symptoms to be discussed in this article have been brought to the notice of pediatrists very forcibly by Finkelstein and termed by him "alimentary intoxication." Of late, others have grouped these cases under the term "acidosis." Finkelstein's alimentary origin of this condition has not by any means been proven, and as to the acidosis, we have seen many patients who had no diminished carbon dioxid in the blood. This latter fact has been noted by Schloss [1] and others. We have, therefore, been most careful in the selection of our title, for even the intestinal origin of this condition has not been proven.

The symptom complex is always associated with gastro-intestinal symptoms, and seems to occur almost wholly in the summer months, seen in our hospital wards from July to September, and most frequently during July and August. It does not seem to be much more prevalent during extremely hot summers and does not resemble the cases of heat stroke in infants. Males and females are equally affected. Prematures, or those congenitally weak, seem more prone to this condition than the strong and vigorous, for five out of our series of twenty-three cases were in prematures. It is relatively rare in children when the hygiene and living conditions are good, for we have never seen it occur in the better class of private practice. It is, perhaps, less common in very early infancy, occurring infrequently before the fourth month and most often between the sixth and tenth months. This may be due firstly, to the fact that usually more than one gastro-intestinal upset has occurred before the toxic symptoms supervene, and secondly, that the purely breast fed infant is almost immune from this condition. The age incidence is rather in contradiction to Ylppo [2] who seems to think that the new-born has a predilection to acidotic conditions. Yet Seham [3] was unable to confirm this. In

1. Schloss, O., and Stetson, R. E.: Am. J. Dis. Child. **13**:218 (Feb.) 1917; Schloss, O.: Am. J. Dis. Child. **15**:165 (Feb.) 1918.
2. Ylppo, A.: Ztschr. f. Kinderh. **14**:268, 1916.
3. Seham, M.: Am. J. Dis. Child. **18**:42 (July) 1919.

our series, all subjects, but one, were in babies artificially fed. This one was an infant, aged 6 weeks, born congenitally weak, and much under weight.

In many instances there was a history of difficult feeding and numerous attacks of diarrhea, yet in some of our cases the history was relatively free from intestinal upsets and the child was doing perfectly well on its formula.

However, in every case gastro-intestinal symptoms were present or had been present before the toxic symptoms occurred. Usually, the child began with an ordinary diarrhea, with a few lumpy and loose movements. This continued either for a few days or a few weeks before vomiting began. At times vomiting and diarrhea began almost simultaneously, the stools becoming gradually more and more frequent and the vomiting persisting. The toxic symptoms usually began a few days or even weeks after the onset of the diarrhea. These were ushered in by restlessness and irritability and followed by apathy, semi-coma and coma.

The children present a picture of being acutely and seriously ill. The skin has an ashen gray, slightly cyanotic appearance, hangs in folds, later frequently becoming scleremic. The fontanel is sunken, upper lids falling over the eyeball, at times resembling a complete ptosis. The cornea is dry and in young infants the iris changes from its characteristic light blue to a brownish gray.[4] The tongue and the mucous membranes of the mouth have a reddish hue.

The respirations in some cases are apparently normal. In others, they are rapid and shallow, and in still others there is present the typical hyperpnea or deep breathing so frequently described. The rapid respirations may be present without any physical or roentgen signs of pneumonia and hyperpnea present or absent, with or without a low carbon dioxid content of the blood. In some cases there may be a complicating pneumonia, but this is not usual. In our cases it was interesting to note how negative the physical examinations were. The heart rarely presented any adventitious sounds. The electrocardiograph was usually normal showing only an occasional tachycardia. The spleen was rarely palpable and the liver was only moderately enlarged.

The nervous system was markedly affected—irritability, then apathy, finally coma and unconsciousness being the rule. Convulsions were not frequent, and if present they were usually terminal. No abnormal reflexes were noted.

Fever was present in most of the cases. It was very irregular and often very high, extending over many days, although absolutely

4. Schindler, E.: Ztschr. f. Kinderh. **19**:153, 1919.

no physical signs could be elicited in the way of complications referable to the ear, lungs or the pelvis of the kidney. The temperature was not influenced by the withdrawing of food nor was it lowered by the administration of fluids. Many of the terminal temperatures were very high, reaching 106 F. In a few cases observed only a few hours or days, in which the entire history was very short, there was a subnormal temperature.

The vomiting was usually most persistent and occurred with any form, kind and quantity of food given. The vomiting usually consisted of the ingested food; blood was never seen. Gavage and lavage were of no avail.

The stools were either very watery and frequent, or full of mucus and green; although it was not unusual to have them become almost normal in color and consistency and yet the toxic symptoms continue. Blood was not often present.

The urine was reduced in amount in every case—more than could be accounted for by the diarrhea and vomiting. Even after many subcutaneous and peritoneal injections the quantity excreted was very small. It seemed to us that the quantity of urine excreted was often directly proportionate to the severity of the symptoms, yet there seemed to be no direct relation between the quantity excreted and the blood findings. We hope that during the next summer we shall be able to report more accurately on twenty-four hour quantities in these cases. The specific gravity was usually high and albumin and casts were found in most cases. Sugar (Fehlings), acetone and diacetic acid were present at times, often, however, they were absent, regardless of the amount of voluntary and involuntary starvation and the severity of the symptoms. Excessive amounts of uric acid and ammonium urate crystals [5] were found in a few cases and are thought by some to signify a bad prognosis. Indican was present in considerable quantity in some cases. The percentage of ethereal sulphate to total sulphates was greatly increased in three cases examined. The kidneys in one case, in which there was almost complete anuria and high retention of nitrogen in the blood, were examined histologically (Dr. Baehr) and found to be practically normal. In this same case the liver was fatty, and there was a marked congestion of the gut.

The duration of this condition varies; at times it is very virulent and lasts but a few days; again, it may last from three to four weeks with periods of marked improvement.

The prognosis is bad; nineteen out of twenty-three patients died (87.5 per cent.). This agrees with Schloss, Hamburger [6] and others.

5. Morgenstern, K.: Ztschr. f. Kinderh. **19**:129, 1919.
6. Hamburger, R.: Jahrb. f. Kinderh. **93**:25, 1920.

ANALYSIS OF BLOOD AND URINE OF CASES OF TOXIC SYMPTOMS OCCURRING IN INFANTS AND CHILDREN

No.	Age in Mos.	Sex	Days Sick in Home	Days Sick in Hospital	Blood — Carbon Dioxid, Volume per Cent.	Urea N, Mg. per 100 C.c.	Incongulable N, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Cholesterol, per Cent.	Sugar, per Cent.	Hemoglobin, per Cent.	Erythrocytes	Leukocytes	Polymorphonuclears	Urine — Albumin	Sugar	Acetone	Diacetic	Microscopic Examination (Casts)	Remarks
1	5	M	19	1	40.4	22.4	62.5	3.0	3.0	...	0.220	··	...	...	··	...	...	...	...	...	Admitted moribund
2	7	M	3	2	41.4	25.2	50.3	1.5	2.8	...	0.095	··	...	...	··	...	...	...	...	...	Premature, no temperature, died
3	10	F	7	20	44.0	19.6	49.0	2.2	1.3	...	0.112	78	5,500,000	9,400	64	Faint trace	Negative	Negative	Negative	Positive	Stools good before death
4	10	M	4	4	62.4	15.4	30.8	3.0	1.2	0.100	0.095	86	5,100,000	...	··	Faint trace	Negative	Positive	Positive	Negative	Terminal convulsion
5	8	F	10	1	53.2	24.2	...	...	...	...	...	84	...	7,400	64	Negative	Negative	Positive	Positive	Negative	Premature, died
6	12	F	2	9	42.4 / 43.8 / 62.4	16.8 / 19.6	49.0 / 56.0 / 31.2	2.5 / 2.2 / 2.2	2.2 / 2.2 / 1.8	0.150	0.140 / 0.175 / 0.085	88	...	15,000 / 24,000	34 / 42	Negative	Negative	Negative	Negative	Negative	Premature, home, well
7	11	F	7	11	41.8 / 39.0 / 44.0	49.0	112.7	6.5 / 1.2	2.0 / 2.5	0.100	0.105 / 0.115 / 0.180	72	...	11,000	82	Negative	Negative	Negative	Negative	Negative	Home, well
8	6	M	1	1	42.0	...	94.2	...	...	...	...	92	...	15,000	70	Very faint	Positive	Positive	Positive	Negative	Undernourished, died
9	4	F	2	1	39.2	82.6	119.6	9.0	6.6	...	0.125	...	...	...	··	Very faint	Positive	Positive	Positive	...	Premature, no temperature, died
10	3½	M	18	3	43.3	36.4	81.9	5.0	1.9	...	...	...	...	...	··	Very faint	Positive	Positive	Negative	Positive	Terminal convulsion
11	6	M	5	4	...	39.2	89.8	5.7	3.5	...	0.113	87	4,000,000	...	··	Very faint	Positive	Negative	Positive	Positive	Well developed child, terminal pneumonia
12	8	F	7	29	44.3 / 41.2 / 63.4	50.4 / 71.4 / 71.4	95.5 / 115.5 / 136.0	4.6 / 4.4 / 2.5	2.8 / 4.0 / 2.0	0.100 / 0.150	0.120 / 0.170 / 0.120	...	4,700,000	9,400	58	Very faint	Negative	Negative	Negative	Positive / Positive	Died
13	6	F	6	8	20.0	26.8	63.3	3.0	1.5	...	0.085	...	...	12,000	62	Trace	Negative	Negative	Negative	Positive	Terminal convulsion (premature twin)
14	6½	F	21	17	31.9 / 44.3 / 34.7	11.2 / 16.8 / 21.0	30.9 / 32.3 / 47.8	1.9 / 1.5 / 1.4	1.4 / 1.4 / 1.2	0.160	0.130 / 0.092 / 0.107	71	...	12,000	48	Faint trace	Negative	Negative	Negative	Negative	Undernourished, no temperature, well
15	22	M	4	3	23.3	32.2	66.5	4.5	2.4	...	0.090	112	5,400,000	27,000	88	Trace	Negative	Negative	Negative	Positive	Died
16	1½	F	2	3	30.4	50.4	126.0	5.2	2.8	0.210	0.150	...	...	...	...	...	...	...	...	...	Premature, subnormal temp., died
17	12	F	6	1	28.6	...	97.0	...	...	0.182	0.230	...	...	...	...	...	...	...	...	...	Hospital 2 hours, died
18	7	F	7	1	24.6	113.4	178.5	4.8	3.6	...	0.132	...	...	...	...	...	...	...	...	...	Hospital 2 hours, died
19	5½	M	7	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Hospital 1 hour, died
20	7	M	4	13	30.0 / 29.5 / 32.5	43.4 / 11.2	81.3 / 44.4 / 83.7	2.1 / 2.5	1.2 / 1.8	...	0.264 / 0.133 / 0.070	71	3,500,000	...	...	Trace	Positive	Trace	Negative	Positive	Transfusion, died
21	5	M	14	1	27.4	...	92.1	...	...	...	0.204	...	...	...	...	Trace	Negative	Negative	Negative	Positive	Died
22	5	F	7	2	...	43.4	...	5.7	3.5	...	...	...	...	...	...	Trace	Negative	Negative	Negative	Positive	Died
23	3½	M	5	6	19.5 / 38.5	84.0	152.0 / 147.3	4.6 / 12.5	4.7 / 4.8	...	0.080 / 0.060	...	6,400,000 / 4,800,000	18,000	44	Trace	Negative	Negative	Negative	Positive	Died

In order to ascertain whether there was any relationship between the clinical symptoms and the blood findings, examinations were made of the urea, nonprotein nitrogen, uric acid, creatinin, carbon dioxid, sugar and cholesterol.[7] In this way we have investigated twenty-three cases. Unfortunately, because of the grave condition of some of the cases, the length of time under observation and other circumstances, most of the cases had only one blood examination; yet in every case at the time the blood was taken, the children presented the typical symptoms of apathy, coma, vomiting and diarrhea.

Attempting an analysis, it would seem that we could divide our cases into four groups.

In the first group, the blood in regard to nitrogen partitions, cholesterol, sugar, carbon dioxid content was fairly normal. In one of these cases we did a second examination with the same result. These cases presented a clinical picture not differing from that of the others.

A second group of six cases (for convenience called uremic cases) had a normal carbon dioxid content, but the nitrogen constituents were markedly increased. This increase took in all the nitrogen substances which we examined. One of these patients was ill for over a period of weeks, and in this case we had the opportunity of making three examinations, all giving the same results. The urine in this group was not very different from that in the cases with normal blood findings, except that albumin and casts were more frequently found. That this high nitrogen retention was, perhaps, not due to diminished blood volume alone can be inferred from the fact that in some cases the hemoglobin estimations and red blood cell count were not excessively high.

In the third group, consisting of four cases, the only change from the normal was a diminished carbon dioxid content. The blood sugar and nitrogenous elements of the blood were normal. In one of these cases, a second blood examination was taken when the child was recovering. A normal carbon dioxid and other normal figures were obtained.

A fourth group of seven cases was a combination of the second and third groups—a nitrogen retention with a low carbon dioxid content. These cases presented no clinical difference from the others. In two of these cases we were able to make repeated examinations, one subsequently showing slightly less nitrogenous retention.

---

7. Methods: Urea—urease (Marshall); nonprotein nitrogen—digestion and titration; uric acid and creatinin with Kuttner's modification of Folin's method; sugar—with Epstein's modification of Benedict's method; cholesterol—Bloor's method; carbon dioxid—Van Slyke's gasometric method.

Schloss also made a number of blood examinations in this type of case and found that the cases could be divided into much the same groups.

In the course of our examination for the uric acid content of the blood, it was noticed that after precipitating the uric acid with silver lactate mixture, the color obtained with the filtrate, using only the phosphotungstate, was exceptionally intense when compared with the filtrate from normal cases. This was noted in some of the cases in which there was no nitrogen retention. Whether this reaction is due to phenol [8] we are not prepared to say. Further investigation relative to the recent work of Tisdall [9] with the phosphotungstic-phosphomolybdic reagent and its bearing on phenols, is being pursued.

From the above it would appear that in some cases the blood chemistry is normal; in others there is a diminished carbon dioxid content; in still others only a retention of nitrogenous products and no acidosis, and finally, there is a group with both a nitrogenous retention in the blood and an acidosis. Most likely the underlying factor is the same in all groups.

Finkelstein [10] and his co-workers have ascribed this toxic symptom complex to the absorption of some of the food principles through a damaged or undamaged gut.

Escherich,[11] Libman,[12] Davidson [13] and many others have tried to ascribe some of these cases as being due to an invasion of a streptococcus or organisms of the dysentery group.

Recently Moro,[14] Bessau [15] and their co-workers have shown that there is an invasion of the duodenum by the *Bacillus coli* in these cases. They believe that these symptoms may be due to the action of these bacteria on the food or to the absorption of products of the bacteria themselves. Pursuing this idea further, Plantenga [16] in Holland and Hamburger [6] in Berlin, treated these patients with subcutaneous injections of a polyvalent *B. coli* horse serum with encouraging results.

In our treatment, the main object was to maintain the water balance, the etiology and the processes of this condition being as yet poorly understood. Glucose solution was used partly for nutrition and partly as a diuretic. Sodium bicarbonate solutions were not used, for it

8. Folin, O., and Denis, W.: J. Biol. Chem. **12**:239, 1912.
9. Tisdall, F. F.: J. Biol. Chem. **44**:409, 1920.
10. Finkelstein, H.: Lehrb. d. Säuglingskrankh. 1911, Part 2, pp. 189-279.
11. Escherich, T.: Jahrb. f. Kinderh. **49**:137, 1899.
12. Libman, E.: Centralbl. f. Bakteriol., Parasitenk. u. Infektionk. **22**:376, 1897.
13. Davison, W. C.: Bull. Johns Hopkins Hosp. **31**:225, 1920.
14. Moro, E.: Jahrb. f. Kinderh. **84**:1, 1916.
15. Bessau, G., and Bossert, O.: Jahrb. f. Kinderh. **89**:213, 269, 1919.
16. Plantenga, B. P. B.: Jahrb. f. Kinderh. **86**:175, 1917.

seemed useless to try to combat the carbon dioxid content only temporarily, and, secondly, the carbon dioxid content was frequently normal.

The food was breast milk or protein milk. In most cases no food seemed to be tolerated in any amount. In one case, a malt soup mixture seemed to do no harm. The fluid of the body was mostly maintained by means of subcutaneous and intraperitoneal injections. Transfusion was only done once so that we cannot report on its value.[17]

CONCLUSIONS

1. These cases seem to occur almost wholly in the summer months and are very rare in entirely breast fed children.

2. These cases are always accompanied by vomiting and diarrhea.

3. The etiologic factor or factors are as yet unexplained.

4. The carbon dioxid content and the nitrogenous constituents of the blood may be normal. Some of these cases may show only diminished carbon dioxid content. Others show a normal carbon dioxid content, but a markedly increased retention of the nitrogenous constituents, and, finally, some cases show both a diminished carbon dioxid content and a nitrogenous retention. Therefore, our studies would indicate that acidosis based on a lowered carbon dioxid content of the blood is not a constant or uniform finding.

The sugar and cholesterol content of the blood may be normal or high. There is apparently no relation between these constituents and either the nitrogenous or the carbon dioxid content.

5. In spite of all the variations in the chemical composition of the blood, there is no difference in the clinical picture or in the history of these cases.

---

17. Since the completion of this paper there has appeared *(Am. J. Dis. Child.* **20**:461 [Dec.] 1920) a very comprehensive paper by Marriott which deals, in part, with acute toxic nutritional disorders. His conclusions are that the toxic symptoms can be ascribed to a water loss from the body and a resulting concentration of the blood. This increased concentration of the blood in acute toxic conditions similar to the above has been confirmed by Rominger *(Ztschr. f. Kinderh.* **26**:23, 1920) who also shows that this concentration persists for a long time during the reparative stage.

DIPHTHERIA AMONG IMMUNIZED CHILDREN.*

S. A. BLAUNER, M.D.
Adjunct Pediatrician, Lebanon Hospital; Medical Director,
Israel Orphan Asylum
NEW YORK

My object in reporting these cases is to have on record the fact that diphtheria can occur among children who possess either natural immunity or who have been immunized by the toxin-antitoxin procedure. If we are to utilize our knowledge of diphtheria immunity intelligently, without prejudice to the community or to the child who has suspicious sore throat, and raise the bars of precautions against a disease of so many possibilities, we must be sure that our interpretative value of a negative Schick reaction will stand the test of time and experience, and particularly that immunity, as obtained by the toxin-antitoxin instillation, is sufficiently universal in its application that not even an occasional exception will alter its value. An immunity recorded by a negative Schick reaction should not be sufficient, and only when a sufficient number of Schick negative immunized children have been exposed to diphtheria contagion and have escaped the disease can a proper value be placed on it. An experience which I and my co-workers have had in a carefully supervised orphan asylum,[1] has taught us that diphtheria in epidemic form can occur among immunized children, at least to say now that the value of a negative Schick reaction is not universal, and as a result further studies and clinical observations must be made before its exact value can be computed.

I am aware that these cases of diphtheria among immunized children are probably the first on record, at least where virulency test was taken, and, therefore, exception may be taken that our experience can be due to either faulty technic, imperfect toxin or antitoxin, or we are even dealing with an epidemic of septic sore throat in diphtheria carriers. All these possibilities have been considered and excluded and with the clinical picture and behavior of the cases there can be no other conclusion but that they were true cases of clinical diphtheria.

The children at the orphan asylum had all been given the Schick test, and our figures correspond so closely with the results of other investigators (40 per cent. positive and 60 per cent. negative) that no fault should be found with either technic or our material. The Schick positive children were all immunized by three doses of toxin-antitoxin,

---

injected at intervals of one week, and after three months they were retested for immunity. A small group, however, still persisted with either a faintly positive or a strongly positive Schick reaction. The weakly positive cases were again tested after a lapse of several weeks, and the few that still reacted, together with the strong positive cases, were given an additional dose of toxin-antitoxin, the latter group receiving, however, a somewhat stronger dose than the three previous doses.

TABLE 1.—Findings with Schick Test in Sixty Cases

	Reaction	Number	Per Cent.
First test..........................	Negative	36	60
Second test......................	Positive	24	40

Table 2 shows that two of the positive cases became negative fifteen months aften the T-A injections.

TABLE 2.—Time of Toxin-Antitoxin Injection and Schick Control of the Twenty-Four Positive Cases

	Date	22 Cases	2 Cases
Schick I..........................	3/25/19	Positive	Positive
T-A 1.............................	4/18/19	....	....
T-A II............................	4/25/19	....	....
T-A III...........................	5/ 2/19	....	....
Schick II.........................	8/ 1/19	Negative	Positive
Schick III........................	12/20/19	Negative	Positive
Schick IV........................	4/21/20	Negative	Positive
Schick V.........................	8/19/20	Negative	Negative

In this manner all our children were finally made Schick negative with the exception of two, who remained persistently positive even after additional tests. It is interesting to note, however, that in the last Schick test made on all the children, August, 1920, these two positive cases, after a lapse of fifteen months from the time the three toxin-antitoxin immunizing injections were given, finally became Schick negative. The question naturally arises whether the toxin-antitoxin had any influence on this end result or whether it was due to the general tendency of natural immunity which the human organism acquires as it grows older. My own impression is that the toxin-antitoxin had no part in the Schick test results, for experience has shown that the toxin-antitoxin shows its influence usually within from three to four months after its injection.

It is our practice to make throat cultures of all new admissions to the observation ward where they remain at least three weeks, depending, of course, on whether any contagion has appeared among them, and when finally admitted to the dormitories as permanent inmates, we are certain they are diphtheria-carrier free. As a further precaution, all

permanent inmates are cultured at least once a year, sometimes oftener, depending on conditions, and as a result of this precaution, we feel that we are at all times free from diphtheria carriers.

Our food supply is regulated and under constant supervision to make sure that no contamination occurs; our milk supply, particularly, is thoroughly supervised and comes from a reputable dealer of this city. The children throughout the institution receive the same food and no outside food, particularly from friends and relatives who are allowed to visit but several times a year, is permitted, so that an infection, such as diphtheria or streptococcus sore throat, occurring from this source would be more or less evenly distributed throughout the institution and not confined to one dormitory as has occurred with this outbreak of diphtheria.

This outbreak of diphtheria was limited to one dormitory consisting of twenty-nine children. In all we had eight cases, beginning with three cases and spreading at intervals of from one to several days until eight children were ill (Table 3). Clinically, the appearance of the membrane, its location on tonsil and pharynx, moderate temperature, absence of toxic symptoms, which are usually present in a tonsillitis or a septic sore throat, gave the impression of a diphtheria throat, but as we had no suspicion that diphtheria can be possible in immunized children, antitoxin was not injected till the report as to the cultures was returned. When it became evident that we were probably dealing with diphtheria infection, we injected these three children, but waited with the prophylactic injections on the other children till we could test for the virulency [2] of these positive cultures.

In the meantime, before the report of the virulency test was returned, the infection continued to spread at intervals of from twenty-four to forty-eight hours until we had a total of eight cases. Clinically, these additional cases showed diphtheritic throat, positive cultures and when the virulency test later returned positive we were sure that we were dealing with a positive Klebs-Loeffler infection. It is also interesting to note (Table 3, Schick III, 12/20/19, in Table 2) that given the Schick test and which showed results similar to those obtained on previous tests, thereby eliminating the possibility of some Schick negative reactions having turned to Schick positive. It is also interesting to note that four children possessed a natural immunity, and three children had an acquired immunity as the result of the antitoxin injection and one child was positive up to the time the infection occurred.

---

2. Cultures and virulence tests were made by the New York City Board of Health. Not only taken by department but under special supervision of head of department.

TABLE 3.—CLINICAL RECORD OF DIPHTHERIA CASES

Case	Name	Age	Date of Onset	Class	Membrane; Location and Character	First Temperature	Temperature 12 Hours after Anti-toxin	Temperature 24 Hours after Anti-toxin	Cultures			Virulence
									I	II	III	
1	M. S.	3 yrs. 8 mos.	12/23	A	Thin, grayish, involving both tonsils and the pharynx	102.8	101.2	100.6	Positive 12/24/19	Negative 1/15/20	Negative 1/20/20	12/31/20 Positive
2	R. P.	4 yrs. 8 mos.	12/23	B	Pharynx and left tonsil; grayish, thick, unbroken	103.0	102.4	101.0	Positive 12/24/19	Negative 1/15/20	Negative 1/20/20	Positive
3	M. M.	5 yrs. 5 mos.	12/23	B	Right tonsil and pharynx; in patches	103.0	102.6	102.0	Positive 12/24/19	Negative 1/15/20	Negative 1/20/20	Positive
4	A. G.	3 yrs. 6 mos.	12/26	A	Both tonsils; pultaceous, dirty gray	104.0	102.0	101.8	Positive 12/24/19	Negative 1/15/20	Negative 1/20/20	Positive
5	L. S.	3 yrs. 9 mos.	12/28	C	Right tonsil; in patches	102.2	100.0	99.0	Positive 12/28/19	Negative 1/15/20	Negative 1/20/20	Positive
6	M. S.	5 yrs. 2 mos.	12/29	B	Both tonsils; pultaceous	102.2	101.0	100.0	Positive 12/30/19	Positive 1/15/20	Negative 1/20/20	Positive
7	H. S.	2 yrs.	12/30	A	Unbroken grayish; spreading over both tonsils and across pharynx	102.4	104.8	103.4	Positive 12/31/19	Negative 1/15/20	Negative 1/20/20	Positive
8	B. S.	2 yrs. 8 mos.	12/31	A	In patches; involving both tonsils and pharynx	103.0	103.0	102.0	Positive 12/31/19	Negative 1/15/20	Negative 1/20/20	Positive

A = Children naturally immune.
B = Children immunized by T. A.
C = Children with persistent positive Schick reaction.

The main possibility to exclude in this epidemic is that these were cases of streptococcus sore throat in diphtheria carriers. It is difficult to understand, however, how we can include streptococcus sore throat, when we consider that all these cases occurred in one dormitory, with the supply of food the same throughout the institution. Furthermore, these children did not behave as children do who have a septic sore throat, neither was the appearance or location of the membrane, which was present in several cases on the pharynx as well, the same, nor was the intensity of the subjective symptom the same; and, what is most important, they all showed a virulent Klebs-Loeffler bacillus which disappeared a reasonable time after injection of antitoxin. We have here, then, I am sure, all clinical and laboratory evidence of a positive diphtheria infection.

CONCLUSIONS

In conclusion, permit me to reiterate that these eight cases are strong evidence that immunization is not absolutely proof against clinical diphtheria, and that we were dealing with a true Klebs-Loeffler infection for the following reasons: (1) character of the membrane, —dull gray, no surrounding hyperemia; (2) absence of prostration, —children were playful, while in septic sore throat infection the prostration is intense, out of all proportion to local involvement; (3) the disease was limited to one dormitory. In septic sore throat, food borne disease usually would have been more evenly distributed throughout the building; (4) occurrence of cases—gradually, from day to day. In septic sore throat, the onset would have been more or less simultaneous. (5) Positive virulent cultures were obtained in all cases which turned negative approximately two weeks after antitoxin injection; (6) absence of positive cases in other dormitories; (1) if these were merely persistent diphtheria carriers with no clinical reaction, it is fair to assume that some should remain so even after injection of antitoxin; (8) immediate improvement of cases on receiving antitoxin; (9) immediate cessation of spread of the disease on administration of prophylactic doses of antitoxin to exposed children in the same dormitory. (10) Is it possible that streptococcus sore throat would have attacked only carriers and avoided the noncarriers?

EOSINOPHILIA OCCURRING IN CHOREA*

HARRY CALVIN BERGER, M.D.

KANSAS CITY, MO.

There are few subjects about which so much has been written and said, and yet so little is understood as about chorea. Until the etiology of this disease, or symptom, as the case may be, is determined, we can hope for little headway. It is with a desire to add a bit of evidence along such lines that I present this preliminary report of work I am undertaking.

Kowalewsky was probably the first to suggest syphilis as the etiology of chorea. Milian [1] then presented two cases with positive Wassermann reactions, and by 1914 he became established in the opinion that all chorea is syphilitic in origin.[2] Comby [3] challenged this theory, contending that a positive Wassermann reaction is no better evidence in favor of syphilis as the cause of chorea, than a positive tuberculin reaction is that tuberculosis is the cause. Guillian pointed out that the pathology in chorea is not that of syphilis of the nervous system, nor do they act the same clinically.

Foti [4] in seventeen cases reported only one case as being free from syphilitic taint. In only thirteen cases, however, was syphilis unmistakable. He considers syphilis as being the principal predisposing factor in chorea, causing instability of the nervous system to such a degree that diverse causes, such as infections, emotional stress, or metabolic disturbance may bring on chorea. Babonneix [5] and Grabois,[6] reviewing 145 and 136 cases of chorea, respectively, from the service of Hutinel, found slight or at least insufficient evidence that syphilis was the origin. Koplik,[7] in 1914, examined ten cases, eight of which gave a negative Wassermann reaction. In the remaining two cases the results were unsatisfactory, though not positive.

1. Milian: Bull. et mém. Soc. méd. d. hôp. de Par. **33**:955, 1912; ibid. **34**:628, 1912.

2. Milian: Bull. et mém. Soc. méd. d. hôp. de Par. **37**:368, 1914.

3. Comby: Bull. et mém. Soc. méd. d. hôp. de Par. **39**:238, 1915.

4. Foti, P.: Pediatria **27**:579 (Sept.) 1919; abstr., Arch. Pediat. **37**:461 (Aug.) 1920.

5. Babonneix: Bull. et mém. Soc. méd. d. hôp. de Par., Series 3 **34**:671, 1912.

6. Grabois: Thése de Paris, 1913, No. 298.

7. Koplik: Arch. Pediat. **32**:561, 1915.

The great mass of evidence is against syphilis as a constant factor in chorea.

Some good results in the treatment of chorea with arsphenamin, even in cases proven nonsyphilitic, have been reported by Bokay, Haines, Hohn and Salinger,[8] Szametz,[9] Marie and Chatelin.[10] Flatau reported unfavorably on this method of treatment. Koplik reported the treatment of nine cases with arsphenamin. In seven he could see no effect. Of the remaining two cases, one developed nephritis and one had a relapse.

The seeming close relationship of rheumatism, endocarditis, and chorea, and accepting as we must the bacterial origin of endocarditis at least, and the frequency with which focal infections are found to exist with these diseases, draws one's attention toward bacterial infection as a causative factor in chorea also.

Westphall, Wassermann and Malkoff [12] and Poynton and Payne [13] reported isolating a diplococcus from the spinal fluid, with which they were able to produce endocarditis, pericarditis, arthritis, or twitching in animals by intravenous inoculation. Donath [14] reported *Staphylococcus pyogenes aureus* and *S. Albus* isolated from the spinal fluid during life in a case of chorea. Collins [15] reported a case cured by an autogenous vaccine made from a coccus in the spinal fluid. Passini [16] was unable to get any growth from the spinal fluid in five cases.

We have had reports of bacilli, staphylococci, diplococci, streptococci, diplococci in chains, and diphtheroids being isolated from the blood of chorea patients. Moderate agglutination of some of these organisms by the blood from chorea patients has been claimed by Camisa.[17] Collins [15] found a diplococcus, and Richards [18] and La Fetra [19] report two cases each of *Streptococcus viridans*. Koplik was unable to isolate any organism after many attempts.

In 1918 Quigley [20] wrote on the bacteriology of chorea, and Cronk [21] on the relation between rheumatism and chorea. Morse and Floyd,[22]

8. Salinger: München. med. Wchnschr. **58**:25, 1912.
9. Szametz: München. med. Wchnschr. **59**:2333, 1912.
10. Marie and Chatelin: Bull. de l'Acad. de méd. Par., Series 3 **68**:507, 1912.
11. Flatau: München. med. Wchnschr. **59**:2102, 1912.
12. Wastphall, Wassermann and Malkoff: Berl. klin. Wchnschr. **36**:638, 1899.
13. Poynton and Payne: Lancet **2**:1760, 1905.
14. Donath: Ztschr. f. d. ges. Neurol. u. Psychiat. **4**:91, 1910.
15. Collins: Brit. M. J. **1**:220, 1913.
16. Passini: Wien. klin. Wchnschr. **27**:1363, 1914.
17. Camisa: Centralbl. f. Bacteriol. **57**:99, 1910.
18. Richards: J. A. M. A. **62**:110 (Jan. 10) 1914.
19. LaFetra: Arch. Pediat. **32**:135, 1915.
20. Quigley, W. J.: J. Infect. Dis. **22**:198 (March) 1918.
21. Cronk: Lancet **2**:646 (Oct. 11) 1919.
22. Morse and Floyd: Am. J. Dis. Child. **12**:61 (July) 1916.

in 1916, reviewed the literature to that date quite thoroughly, and reported their own studies on blood and spinal fluid cultures, with some animal inoculations, in a series of twenty-six cases of chorea. They reached the following conclusions: "Our investigations show that syphilis plays no direct part in the etiology of chorea. Our results suggest that a micro-organism or group of micro-organisms may be the cause of chorea. They seem to show that if chorea is caused by a micro-organism, the source of infection is ordinarily in the tonsils or teeth. They tend to confirm the belief that there is an intimate relation between chorea, rheumatism and endocarditis."

In 1916, Goodman [23] reported some favorable results from auto-serum therapy. Since that time Moffett,[24] Faber [25] and Brown, Smith and Philips [26] have reported their results with his method of treatment.

Porter [27] used horse serum in place of autoserum intrathecally with some good results. Haneborg,[28] in 1916, gave a report on the treatment of chorea with thymus gland, suggesting the possibilty of a disordered thymus function playing a rôle in the etiology of chorea.

The literature yields surprisingly little on the study of the blood in chorea. No other disease that occurs with the frequency of chorea, and with such distressing symptoms, has had so little attention paid to the blood. Cabot [29] says: "Chorea showed in twelve cases normal blood, except for increased percentages of eosinophils, as in Zappert's two cases which Louga confirms." Brown,[30] making twelve observations on two cases of chorea noted an eosinophilia varying from 5.2 to 9.5 per cent.

Macalister [31] found in his first two cases examined, 20 and 16 per cent. eosinophils, respectively, and in later cases found an eosinophilia in all but one case. The stools were free from ova, and no other explanation could be found for the eosinophilia. Eosinophilia was not present in cases of rheumatism examined by him. Leopold [32] reported twenty cases of chorea, with eosinophilia varying from 1 to 16 per cent. He claims a higher eosinophilia in a second attack of chorea than in a first attack. He found eosinophilia present in a high proportion of cases examined, and could offer no explanation for this except chorea, other causes being sought as far as possible.

23. Goodman: Arch. Pediat. **33**:649 (Sept.) 1916.
24. Moffett: Med. Rec. **92**:414 (Sept. 8) 1917.
25. Faber: Calif. State J. M. **15**:27 (Jan.) 1917.
26. Brown, Smith and Philips: Canad. M. A. J. **9**:52 (Jan.) 1919.
27. Porter, L.: Am. J. Dis. Child. **16**:109 (Aug.) 1918.
28. Haneborg: Norsk Mag. f. Lægevidensk. **77**:1040 (Aug.) 1916.
29. Cabot, R. C.: Clinical Examination of the Blood, Ed. 3, New York, William Wood & Co., p. 313.
30. Brown, T. R.: Maryland M. J., 1902.
31. Macalister, C. J.: Brit. M. J. **2**:514, 1909.
32. Leopold, S. S.: New York M. J. **100**:225, 1914.

RESULTS OF STUDIES OF EOSINOPHILIA IN CHILDREN

Name	High Percentage	Low Percentage	Average Percentage	Remarks
Lena S.	7	7	7.0	Had attack one year ago; tonsils badly infected
Mary S. P.	23	7	15.5	
Mable G.	14	14	14.0	Goiter; no ova in stools
Ettie O.	9	1	4.75	Very mild case
Rose R.	7	3	5.0	First attack; tonsils removed in six weeks
Rose R.	5	1	3.0	Second attack 11 months later; no rheumatism or endocarditis
Ernest A.	17	6	13.25	No ova in stools; marked obesity
Christine P.	7	1.5	3.3	Very severe type chorea major
Mary V.	9	2	4.66	
Lloyd R.	5	1.5	3.17	
Violet M.	9	0	4.5	Clinical syphilis; Wassermann 4 plus
Ernestine M.	13	3	8.0	
Violet W.	9	1.5	3.5	
A. B. S.	5	1	2.75	
Mary S.	11	7	9.0	Had sister in hospital with chorea major several months ago
Margaret W.	9	2	5.3	First attack, another in 8 months
Margaret W.	11	11	11.0	This is second attack, 8 months after first
Helen T.	16	2	7.5	Stools not examined
Ethel C.	4	3	3.41	
Jessie S.	2	2	2.0	
David S.	19	19	19.0	No ova in stools
Valencia P.	13	13	13.0	No ova in stools
Kenneth V. H.	14	7	10.5	No ova in stools) Brothers
Keith V. H.	4.5	1	2.70	No ova in stools) same date
Henry E.	5	5	5.0	
Dolly D.	6	4	5.33	
Thelma A.	14	2	8.36	
Jos. M.	5	2	3.5	
Edith C.	6	3	4.0	
Anna S.	22	8	13.75	
Anna S.	26	18	22.2	
Helen W.	12	2	5.0	First attack; no ova in stool
Mary G.	17.5	11	13.6	Second attack 10 months later; no ova in stool
Elizabeth H.	4	2	2.88	Recovery very slow; stool negative
Dominic P.	18	14	16.0	Stool negative
Margaret G.	18	8	13.0	Last two counts made in O. P. D.
Gertrude M.	7	4	4.88	No examination of stool
John H.	7	7	7.0	No ova in stool
Le Verne S.	1	1	1.0	The following year developed rheumatism and endocarditis
Juanita I.	12	7	9.5	
Dorothy B.	7	3	5.2	
Wilma K.	7	5	5.6	
Hazel Van C.	8	3	5.5	
Average	10.35	5.24		
General average all counts			7.60	

In my series of cases I have paid attention principally to the blood, and in the blood particularly to the percentage of eosinophilia present. It was begun in 1916 and continued to date, except for a period of a few months when I was unfortunately obliged to abandon the work.

In a few cases only a single count was obtained, these cases not being easily available for more counts. It was impossible accurately to determine the period in the disease when each count was taken, as the accuracy of the history as to onset depended entirely on how keen the parents were in observation, and most of these cases were seen on my hospital service, or in the outpatient department clinic. There was no connection between the severity of the symptoms, and the percentage of eosinophils found, a comparatively mild case sometimes giving a much higher count than a very severe case, and in some of my most severe cases, in which restraint was required, a low percentage of eosinophils was noted. Nor did the counts vary regularly before, during, or after some temporary exacerbation of the symptoms. No case was included in which the diagnosis was not perfectly clear. In no case reported here were there any parasites or lesions on the skin or scalp to account for an eosinophilia. A careful examination for intestinal parasites was made on most of these children, in all but one case in which a particularly high count was found. This was omitted in a few cases.

None gave a history of asthma or eczema. A Wassermann examination was made on most of these children. The proportion of positive reactions ran slightly less in this group than in the whole group of patients in this hospital tested, though some were frankly syphilitic clinically as well as having a positive Wassermann reaction. Focal infection in tonsils, and especially teeth, was, of course, common in this class of patients, but not any more so than in the average of patients at this clinic. Rheumatism and endocarditis were peculiarly rare in the histories of these children. The ages ranged from 7 to 14 years.

There were twenty-nine girls and eleven boys. Three girls were seen during both the first and the second attacks, the second attack coming on in the year following the first attack. One girl had a marked goiter. Two boys were brothers and were brought into the hospital at the same time, with chorea of about equal severity. In some cases treatment was begun before the first blood examination, in others not. The type of treatment was not the same in all cases. No autoserum treatment was given.

The blood films were prepared with ordinary glass slides by allowing a drop of blood to follow the edge of one slide along the surface of the other. This gave an uneven streaked end to the film, and this

was always included in the examination of the slide. I found that the eosinophils were in higher percentage in this portion of the preparation than in the main body of the film, a fact that I am at a loss to explain. The stain used was Wright's blood stain—secured from two different sources. To insure greater accuracy each count was of 900 white blood cells, the percentage of eosinophils being calculated from this count.

I have arranged my results in the accompanying table so that it may be seen at a glance just what was fonud.

The table presents my findings so clearly that there seems to be little need for further elucidation. The highest count was 26 per cent., the lowest 0, with a general average of 7.6 per cent. The criticism may be offered that in eight cases, and in a case during a second attack, only a single count was made, and that these counts should not be included in my averages. However, it seemed to me better to do so. Every possible effort to explain the eosinophilia in some way, other than chorea, was made.

I have been unable to make up my mind definitely as to the highest percentage of eosinophils that may be considered normal at a given age, knowing that in children we must allow for higher percentages than in adults. Within the age range here given, you may form your own conclusions in this respect. While some of these cases will easily fall within normal limits, others are far above. Certainly, the general average of 7.6 per cent. must be considered an increase of eosinophils, and I have considered all except five cases showing an eosinophilia some time during the series of counts.

The rise and fall in these counts could not in any way be connected with the clinical progress of the case, and I am at a loss to explain this feature.

What bearing this eosinophilia may have on the etiology of chorea, we are as yet in no position to discuss fully. That chorea is not often, if ever, syphilitic in origin, I believe is generally conceded. If chorea is due to a bacterial infection, whether specific or otherwise, is the eosinophilia due to the sensitization of the child to the invading organisms? Such a theory might be suggested by the work of Floyd and Baker.[33] This is hardly tenable, however, since we do not find this present in rheumatism according to Macalister,[31] nor do we find such an eosinophilia present in other types of general infection.

Is it possibly due to a toxemia as in the case reported by Deglos,[34] where eosinophilia was produced in an anemic patient, with enteritis,

---

33. Floyd and Baker: Boston M. & S. J. **175**:199, 1916.

34. Deglos, E.: Lyon méd. **128**:231 (May) 1919; abstr., J. A. M. A. **73**:231 (July 19) 1919.

through periodic poisoning by carbon monoxid gas from a charcoal stove?

If it is a toxemia, may it not be due to an altered metabolism, resulting possibly from a hyperactivity of one of the glands of internal secretion, or a suppressed inhibition due to deranged or deficient function of such a gland, as Haneborg [28] suggests?

The known effect of the reproductive organs, particularly in the female, on the internal secretions, and the fact that chorea is not an uncommon complication of pregnancy, while not offering an argument, may have some significance in this connection.

To me it seems more probable that if chorea is the result of a general bacteremia, it acts on some body structure, possibly one or more of the endocrine glands, through a toxin or otherwise, than that the infection is a cerebral irritant per se. Such a course of action might also account for the eosinophilia present, through sensitization to a toxin, or to the superabundance of some secretion which is normal and hence gives no reaction in smaller quantities. It does not seem that a straight infection could do so.

Another explanation might be attempted, showing that the abnormal physiology of the nervous system itself reacts on other structures in some way, producing a substance which stimulates eosinophil production.

It is my hope that this preliminary report will stimulate further work on the etiology of chorea.

THE PRESENCE OF SUGAR IN THE URINE OF NEW BORN INFANTS BEFORE THE INTAKE OF FOODS *

FRANCES MILLIKIN

CHICAGO

Czerny and Keller [1] mention that Mesnil found sugar occasionally in the urine of infants during the first few days of life, and Nothman [2] found sugar in the urine of premature infants. The presence of sugar was shown by reduction tests, and in the case of Nothman the osazone was prepared which indicated the presence of lactose. By using the Benedict-Osterberg [3] method, Greenthal [4] showed that the urine of all infants contains sugar. This would be expected from the results obtained by Benedict, Osterberg and Neuwirth.[5] These authors found determinable quantities of sugar at all times, both in the urine of normal dogs, and those fasting for four-day periods, and in the urine of adults.

Thanks to the kindness of Dr. Sauer, we were able to obtain the urine of a series of new born infants for sugar determination.

The urine was collected during the period preceding the first feeding. None of the births was difficult, so that the results cannot be vitiated by the transitory traumatic glycosuria described by Hoeniger.[6] The method employed for the determination was that described by Benedict and Osterberg,[3] which has the important advantage of eliminating the possibility of the interference, in the determinations, of albumin, which occurs in the urine of the newly born. In all instances, duplicate determinations were made, all of which agreed very closely. In every case the urine was strongly acid to litmus. The first five cases are not recorded in the tables. They showed 0.036, 0.034, 0.072, 0.05 and 0.136 per cent. sugar, respectively.

Table 1 shows the quantitative determinations of sugar in the urine of individual infants. In Table 2, combined specimens from two or three infants, as indicated, were used. The amounts of urine per individual varied between 6 and 34 c.c. The amonts of total urinary

1. Czerny and Keller: Des Kindes Ernährung, etc.
2. Monatschr. f. Kinderh. **8**:377, 1909.
3. Benedict and Osterberg: J. Biol. Chem. **34**: 195 (April) 1915.
4. Greenthal: Am. J. Dis. Child. **20**:556 (Dec.) 1920.
5. Benedict, Osterberg and Neuwirth: J. Biol. Chem. **34**: 217 (April) 1915.
6. Hoeniger: Deutsch. med. Wchnschr., **1**: 500 1911.

sugar for the collection period ranged from 1.722 to 27.948 mg., with an average of 9.536 mg. The concentration of sugar in Tables 1 and 2 varied between 0.027 and 0.166 per cent., with an average of 0.078 per cent. Too much importance should not be attached to averages for so few cases.

Benedict, Osterberg and Neuwirth [5] found sugar in the urine of adults collected for two hour periods in the morning before food was taken, in concentrations of from 0.04 to 0.16 per cent. for one subject and from 0.03 to 0.049 per cent. for another. Greenthal [4] showed sugar to be present in the urine collected for eight hour periods from infants on ordinary diets in concentrations of from 0.045 to 0.092 per cent. The twenty-four hour urine of a normal adult on ordinary diet contained from 0.042 to 0.22 per cent sugar, that of another from 0.04 to 0.126 per cent.

TABLE 1.—QUANTITATIVE DETERMINATION OF SUGAR IN URINE OF INFANTS

No. Name Amount	Sp. Gr.	Total Sugar	
		Per Cent.	Mg.
1. Dixon .... 7 c.c.	1.011	0.078	5.467
2. Keck .... 6 c.c.	1.007	0.028	1.722
3. White ....17 c.c.	1.006	0.027	4.607
4. Brewster ....34 c.c.	1.003	0.082	27.948
5. Koran .... 9 c.c.	1.010	0.061	5.540
6. Brown .... 9 c.c.	1.012	0.043	3.906
7. Trueblood ....10 c.c.	1.012	0.051	5.100
8. Nein ....15 c.c.	.....	0.140	21.420
9. Foster ....15 c.c.	1.016	0.100	15.000
10. Perry ....17 c.c.	1.010	0.072	13.308
11. Farnsworth ......11 c.c.	1.010	0.128	14.102
Average .....13.6 c.c.	1.009	0.073	10.738

In Table 3 two determinations of the unfermentable sugar are given. There is sufficient reason to accept the fermentable sugar as glucose, but the nature of the unfermentable sugar is not known. In this table the unfermentable sugar was present in lower percentages (12.6 and 30.8 per cent.) than in the urine of infants and adults on regular diets or in the urine of adults during the fasting period of the day. For example, in urine collected from adults during the two-hour period in the morning before food was taken, Benedict, Osterberg and Neuwirth found unfermentable sugar to constitute from 57 to 73 per cent. (at one time falling as low as 36.3 per cent.) of the total urinary sugar for one subject and from 41.8 to 71.0 per cent. for the other. For adults on mixed diets they found the twenty-four hour urine

specimens to contain unfermentable sugar constituting from 40 to 65 per cent. of the total urinary sugar. Greenthal[4] demonstrated that of the total urinary sugar of infants on ordinary diet, from 38 to 49 per cent. was unfermentable sugar.

TABLE 2.—QUANTITATIVE DETERMINATION OF SUGAR IN COMBINED SPECIMENS OF URINE

No. Name	Amount	Sp. Gr.	Total Sugar	
			Per Cent.	Mg.
12. Horne				
	} 23 c.c.	1.009	0.073	16.88
13. Wells				
14. Pratt				
15. Bang	} 25 c.c.	1.011	0.082	20.55
16. Jones				
17. Friedlander				
	} 21 c.c.	1.014	0.080	16.926
18. Benedict				
19. Blair				
	} 30 c.c.	1.015	0.050	17.4
20. Woodburn				
21. Morgan				
	} 12 c.c.	1.016	0.166	19.92
22. Morganson				
Average ......11 c.c.		1.013	0.090	8.334
Average of Tables 1 and 2....12.3 c.c.		1.011	0.078	9.536

The results of this series of urinary sugar determinations show that sugar does constantly occur in the urine of newly born infants before food is taken, and that it is present in about the same concentrations as in the urine of normal adults before food is taken in the morning.

TABLE 3.—DETERMINATIONS OF UNFERMENTABLE SUGAR

No. Name	Total Sugar Per Cent.	Mg.	Fermented Sugar Per Cent.	Mg.	Unfermentable Sugar Per Cent.	Mg.	Total Sugar Per Cent.
4. Brewster 0.082		27.948	0.0718	24.416	0.0103	3.532	12.6
12. Horne							
} 0.073		16.88	0.051	11.69	0.021	5.191	30.8
13. Wells							

The range of concentrations can easily explain why sugar is sometimes found in the urine of the newly born by the usual copper reduction tests. For instance, Miss Felcher, working with Dr. Woodyatt,[7]

---

7. With the permission of Dr. Woodyatt these data are published.

found that Haines' test gives a positive reaction readily with a concentration of sugar in the urine exceeding 0.07 per cent when 5 c.c. of the reagent and 2 c.c. urine are used.

As in the case of adults, as demonstrated by Benedict, Osterberg and Neuwirth, and of infants, as shown by Greenthal, this urinary sugar can be separated into a fermentable and a nonfermentable portion.

NECROPSY FINDINGS IN NEW-BORN INFANTS *

MARGARET WARWICK

Pathologist to the Miller Hospital

ST. PAUL

Postmortem examinations and the correlation of the findings with clinical phenomena have played a most important rôle in the progress and development of medical science. But only too often the interest in necropsies does not include those performed on new-born infants; instead, deaths in infancy occupy a place similar to the tonsil or appendix in the tissue laboratory, i. e., not examined except under some very important or unusual conditions.

In a previous report[1] I published a survey of routine necropsies performed on new-born infants dying at the University Hospital over a period of three years—a series of thirty-six—in which survey special attention was devoted to the incidence of cerebral hemorrhage. So much interest has been aroused concerning other causes of death that another and more general study from that point of view has seemed advisable. Consequently, a survey of the results obtained in the postmortem examination of infants has been made from the past ten years' record of the department of pathology, including those from the University Hospital. These necropsies were performed by members of the department at the request of various clinicians in various parts of the city, and thus represent not entirely routine examinations but largely those to which some especial clinical interest in regard to either mother or child was attached. Performed as they were by various members of the staff, both past and present, at various times and places and under very different conditions, they lack uniformity in both technic and report of findings. Also in many cases the clinical data were inadequate or unavailable. However, enough significant facts are apparent to stimulate further interest in autopsies on infants and to justify efforts to obtain an examination of every case of death even in infancy.

This series includes 200 necropsies performed on babies who were stillborn or who died a week after birth, thus eliminating to a certain extent postnatal affections. Unfortunately, of the 200, only 136 represented complete examinations, the opening of the skull having been omitted in sixty-three and only the head having been examined in one

1. Warwick: Cerebral Hemorrhage of the New-Born, Am. J. M. Sc. **158:** 95, 1919.

case. Of the total number, 120 were males, seventy-eight were females and the sex was not mentioned in two. One hundred and fifty-two were apparently full term infants, and of these, two (both of whom were stillborn) had a history of having been overdue for about two weeks. Of these full term babies ninety-three were alive at the time of birth; fifty-nine were dead. Forty-eight were probably premature, varying in age from 6 to 8½ months, and of these nineteen were stillborn and twenty-nine lived for some time. Therefore, of the total number, 122 breathed spontaneously and seventy-eight were born dead.

One group of fourteen cases has not been given detailed consideration since they were all coroner's cases representing infanticide and showing evidence of traumatic death unaccompanied in each case by any other evidence of diseased conditions. In yet another case a craniotomy had been performed during a markedly prolonged labor, thus placing this infant in the group of traumatic deaths.

Table 1.—Necropsies Made, Viability of Infants and Lesions Found

		A. Number Done	Per Cent.
Complete necropsies ...:........................		136	68
Head not examined		63	31
Body not examined		1	0.5
Total		200	
B. Viability			
Infants living		122	61
Full term	93		
Premature	29		
Total	122		
Born dead		78	39
Full term ....:.....	59		
Premature	19		
Total	78	200	
C. Findings			
Lesions found		140	70
Traumatism		14	7
No lesions found ....:....		46	23
Head not examined	22		
Premature	16		
Full term	30		
Total	68	200	

In only forty-six of the 200 cases was no gross or microscopic lesion found, but of these forty-six cases the head was not examined in twenty-two, thus rendering impossible the demonstration of some intracranial lesion, such as cerebral hemorrhage—a very frequent finding in new-born infants. Therefore, in only twenty-four of the 200 (12 per cent.) did a complete examination fail to show some demonstrable lesion. In

some of these, premature birth alone might readily have accounted for death; or, there might have been lesions present which were overlooked by the ordinary routine examination. For example, some observers have found that in certain cases the thymus may be so large as to cause very marked compression of the trachea, thus seriously interfering with or preventing breathing. Such a condition, especially when, as often happens, the thymus is not carefully examined, might be overlooked, unless the pathologist is especially well trained.

However, in this series 154 cases, or 77 per cent., did show definite pathologic lesions, even though the examinations were incomplete in some cases. Surely this fact demonstrates beyond a doubt the importance of necropsies on infants, and shows the fund of knowledge which may thus be given to the pediatrician, obstetrician and pathologist. Such a prospect is worthy of the closest cooperation between these specialists and the resulting trend toward more and better scientific medicine.

TABLE 2.—CEREBRAL HEMORRHAGE

			Per Cent.
Stillborn	9	12	
Full term	3		
Premature	3		
	12		
Living		41	
Full term	34		
Premature	7	53	43
	41		
Associated with hemorrhagic disease		20	

Here, as in the shorter series from the University Hospital, the most common finding was cerebral hemorrhage, which occurred in fifty-three cases (Table 2). In the total series only 138 heads were examined, and of these thirteen were those of obviously healthy infants, the victims of infanticide, and therefore only 125 heads were examined in babies dying from natural causes.

Therefore, the fifty-three cases of cerebral hemorrhage found represent a percentage of 42 in all cases of infants either stillborn or dying in the first few days of life, on the bodies of whom a complete examination was made. This number representing, as it does, only cases picked at random by clinicians especially interested in that particular case, compares very favorably with the higher number of 50 per cent. obtained by routine complete necropsies at the University Hospital. In that study it was found that cerebral hemorrhage in the new-born usually presented no distinctive symptoms or syndrome. Therefore,

there are undoubtedly many babies who died because of that condition and yet during life did not attract sufficient attention to justify request for a necropsy or even with a necropsy to make imperative the examination of the brain. It is quite reasonable to conclude that very many of these cases escape a correct diagnosis.

Such figures as these emphasize strongly the attention due such a condition and the value of statistics based on detailed complete and routine postmortem examination of every infant, either stillborn or dying in early infancy. Such a procedure is simplified by the ease with which these permissions are obtained. In many cases, especially in stillbirths, the parents do not require the return of the body following the necropsy. However, even when they do, restoration may be made as satisfactory as in an adult.

Cushing [2] and Strachauer [3] both advise operation as a therapeutic measure in cerebral hemorrhages of the new-born whenever the diagnosis can be made and thus prevent various palsies which may result later in life. In addition, then, to the contribution to general knowledge necropsy studies as to frequency, size and location of these cerebral hemorrhages will be a very real and important aid to the surgeon and may greatly widen his scope of activity in cerebral surgery of the new-born.

It is of great interest to find that of the fifty-three cases showing intracranial hemorrhages, only twelve were stillborn babies while forty-one breathed for some time. In many cases the histories showed that the babies were perfectly normal at the time of birth, the symptoms, when they were present, not appearing for several days. In twenty of these cases the hemorrhage over the brain was associated with hemorrhages in other organs suggesting the syndrome known as hemorrhagic disease of the new-born, which is characterized by an increased clotting time of the blood. This at once brings up the question of the decreased coagulability of the blood being intimately associated with the etiology of the cerebral hemorrhage. One is justified in such an assumption when one finds that nearly one-half of the cases of intracranial hemorrhage are associated with multiple hemorrhages in other organs.

Even in a short, normal labor there must necessarily be great congestion, distortion and, perhaps, laceration of the intracranial blood vessels of an infant. This is emphasized by the anatomic fact that, at this early age, there are no adhesions between the dura and cortex, leaving the delicate blood vessels entirely unprotected as they leave the

2. Cushing: Intracranial Hemorrhage of the New-Born, Am. J. M. Sc. **130:** 563, 1905.

3. Strachauer: Surgical Treatment of Cerebral Hemorrhage in the New-Born, Minnesota Med. **3:**577, 1920.

surface of the brain. It is reasonable to believe that, although injury frequently occurs, the hemorrhage is small, soon ceases and is finally absorbed in a normal infant. But should the coagulation time of the blood be increased, the hemorrhage may attain great size and finally cause either death or the distressing palsies or contractures too often appearing later in life.

From these findings, as well as those of the former shorter series, one is convinced of the fact that intracranial hemorrhage is a common condition in new-born infants and is often associated with and frequently caused by hemorrhagic disease in the new-born. Further complete routine postmortem examinations on every dead infant will add valuable knowledge to our conceptions of both these conditions as well as their relationships to each other.

TABLE 3.—HEMORRHAGIC DISEASE AND SINGLE HEMORRHAGE

A. Hemorrhagic Disease			Per Cent.
Associated w i t h cerebral hemorrhage		20	10
Associated with congenital syphilis		7	3½
Associated with malformations		4	2
Associated with ulcerations		3	1½
Duodenum	1		
Hard palate	2		
Occurring alone		7	3½
Total		41	20½
Clinical symptoms	13		
Head not examined	5		
B. Cases Showing Single Hemorrhage			
Lungs		5	2½
Liver		2	1
Thymus		1	½
Suprarenal		1	½
Total		9	4½

The lesion ranking second to cerebral hemorrhage, both in numbers and importance, is hemorrhagic disease of the new-born considered as an entity by itself. This most important condition has recently been brought into great prominence by Rodda[4] in his study dealing with diagnosis by means of routine determinations of coagulation of the blood carried out by his simple method and, when found, treatment of the disease by means of subcutaneous injections of whole blood.

In this series, forty-one, or 20 per cent., gave evidence of this condition (Table 3), and of these forty-one, only thirteen showed the clinical sign of prolonged bleeding from an abrasion or hemorrhage

---

4. Rodda: Studies with a New Method for Determining the Coagulation Time of Blood in the New-Born, Am. J. Dis. Child. **19**:269 (April) 1920.

from the mucous membranes. But doubtless had a coagulation time been done the clinical diagnosis would have more closely approximated the autopsy diagnosis.

Of the forty-one bodies showing the multiple hemorrhages, twenty, or one-half, showed also intracranial hemorrhages as mentioned above. In five cases no examination of the brain was made, so had more complete necropsies been performed a yet larger number might have shown hemorrhage over the brain. Since about one-half of the cases of hemorrhagic disease showed cerebral hemorrhage, there is very strong evidence that in many cases the two conditions must be very closely related.

In only seven of these forty-one was there evidence of syphilis. Only four were associated with malformations or developmental defects. This observation is of interest only in the consideration of the possibility of hemorrhagic disease coming under the head of developmental defects and, therefore, being associated with other malformations—a supposition not borne out in this study.

Of great interest, however, is the finding in three of these cases, and in no others in the series, of ulcerations of the mucous membranes from which there was apparently prolonged bleeding judged by the adherent thrombi. One of these ulcers was in the hard palate, the other two ulcers were in the duodenum. One is accustomed to seeing duodenal ulcers associated with hyperacidity in adults but duodenal ulcers in infants is a rare finding. However, since no similar findings were observed in other cases, and since these three cases showed multiple hemorrhages in the viscera as well as clinical signs of bleeding from the mouth and bowel, one is justified in the belief that the ulcerations were the results of the pre-existing hemorrhagic diathesis. This theory is strengthened by the fact that these infants lived three, four and five days, respectively.

Nine other bodies revealed large hemorrhages in single organs—five in the lung, two in the liver, and one each in the thymus and suprarenal. But these cases were not included in the list showing the hemorrhagic syndrome because of the strong possibility of single hemorrhages being due to trauma resulting from birth or artificial respiration.

The next group claiming attention is the ever interesting one of malformations. Of the 200 cases studied, thirty showed developmental defects, and in only eight of the thirty were multiple malformations noted. Therefore, contrary to the belief that malformations usually are multiple, less than one-quarter of the cases of this series followed that rule (Table 4). The majority of these are listed in the table and need no farther explanation. Many of the more common ones appear but once. The case of transposition of the viscera was complete in every detail. Polycystic kidney occurred twice and both were extreme cases. Each one showed a normal liver. Two most striking anomalies of the

TABLE 4.—MALFORMATION

		Per Cent.
Heart		
Opening in interventricular septum.........	4	
Very large opening in interauricular septum	1	
Bifid apex	1	
Four cusps on aortic valve.................	1	
Absence of interventricular septum and pulmonary artery	1	
Pulmonary artery continuous with aorta....	2	
Atresia of pulmonary vein	1	
Aorta of pulmonary from right ventricle.....	1	
Total	12	6
Gastrointestinal tract		
Atresia of small intestine..................	4	
Stricture of esophagus	2	
Subhepatic position of colon...............	1	
Total	7	3½
Urinary tract		
Absence of right kidney, ureter, urethra and anterior abdominal wall..................	1	
Double kidney and ureter	1	
Atresia of ureters at bladder orifice..........	1	
Hydronephrosis and hydroureters (bilateral)	3	
Hydronephrosis and hydroureter (unilateral)	1	
Horseshoe kidney	1	
Malformed kidney	1	
Polycystic kidney	2	
Total	11	5½
Liver		
Hemangioma	1	
Malformed liver	1	
Total	2	1
Suprarenals		
Accessory suprarenal	1	
Aplasia of suprarenals	1	
Total	2	1
Brain and spinal cord		
Hydrocephalus	2	
Iniencephaly	1	
Anencephaly	1	
Encephalomeningocele	1	
Encephalocystocele	1	
Spina bifida with hydrocephalus	2	
Total	8	4
Transposition of viscera	1	
Cleft palate	1	
Hare lip	1	
Club feet	1	
Accessory spleen	1	
Stenosis of larynx	1	
Total cases, 30.		
Multiple, 8.		

heart were seen; one case showing only one single large ventricle and leading from it one large artery which gave off branches to the lungs and then followed the usual aortic course. The other had a blind end to the pulmonary vein and no vessels communicating with the left ventricle, the only opening being in the interventricular septum. The other malformations of the heart were those which are usually seen.

Atresia of the small intestine was observed four times. In each case there was no-complete interruption of continuity, but a solid cord connected the two patent ends of bowel. One of these cords was found in the lower end of the small intestine at a point corresponding to the frequent site of a Meckel's diverticulum; in a second case the cord was at the junction of duodenum and jejunum; in a third, it was 75 cm. below the pylorus and was associated with a definite break in the mesentery; and in the fourth case it was in the duodenum. Congenital stricture of the esophagus occurred twice and stenosis of the larynx once.

TABLE 5.—BIRTH INJURIES

		Per Cent.
Fractured vertebrae (3rd, 4th and 5th).........	3	
Fractured skull	1	
Dislocated occipital bone	1	
Torn tentorium	1	
Ruptured mediastinum........................	1	
Total	7	0.3½

There was a comparatively large number of malformations of the head and spinal cord, due, perhaps, to the fact that these were unusual, attracted attention and were sent to the university because they were thought to be of special interest. The percentage of necropsies on such cases is, therefore, much higher than would result from routine examinations of every dead infant.

For the same reason, there are a large number of birth injuries. A long, abnormal or otherwise unusual labor resulting in a stillborn child or one dying soon after birth excites the interest and suspicion of both the obstetrician and the relatives, and a necropsy is requested. In this series birth injuries were seen seven times (Table 5). The most common injury was fracture of the vertebrae, which occurred three times in the third, fourth and fifth vertebrae, respectively, and in each case, as would be expected, there was a laceration of the spinal cord at that level. A fractured skull was seen only once, as was also one case of dislocation of the occipital bone causing a fatal hemorrhage, one example of a tear in the tentorium, and one instance of a ruptured mediastinum with resulting emphysema and pneumothorax. However, even considering the number of birth injuries as being larger here than

in routine series, it is still very small, representing as it does less than one-half of 1 per cent.

Congenital syphilis was found twenty-three times, and in only thirteen cases were signs or symptoms in the parents given in the history. However, it must be borne in mind that the majority of these histories were obtained by the pathologist under adverse conditions, and are consequently, in many instance, at least, neither complete nor reliable. On the other hand, in eight cases the parents gave signs of syphilis but no demonstrable evidences of syphilis were found in the necropsy on the child. In this latter group the infants might have escaped the disease, although in some cases, at least, the presence of the disease may have been overlooked or may have been in a latent form. Syphilitic lesions frequently do not stand out very prominently and may appear only in the microscopic picture, and only too often this is complicated or obscured by the pronounced autolysis or postmortem changes having taken place either before or after birth. An examination of the epiphyseal line may be of definite value, but cannot always be carried out without an unwarrantable mutilation of the body. Congenital syphilis may easily be overlooked unless a careful and detailed search be made on a body which has not yet undergone too marked postmortem changes.

It is of interest to note that in the nineteen cases showing evidences of congenital syphilis, only two bodies were in a macerated condition, while nine other bodies without either findings or history of syphilis showed maceration. While it is an undisputed fact that causes other than syphilis may produce death of the fetus in utero, it must be admitted that in many instances maceration may have obscured the evidence of syphilis, and that since many of these histories were incomplete or inadequate the condition may have been really present in a larger percentage of cases than is shown by this analysis.

In such a series as this, consisting of infants dying within a week of birth, very few acute infections were found. In the case of one baby, living six days, death was caused by infection of the umbilical stump. In the case of another baby living only twelve hours, a marked vegetative mitral and tricuspid endocarditis was found. Since the infant showed evidences of congenital syphilis and the mother gave a history of a recent rash typical of the secondary stage of syphilis, this was considered to be an acute syphilitic lesion of the heart valves. However, as there had been no opportunity at this necropsy to make careful bacteriologic studies, the possibility of this being a streptococcic infection superimposed on a syphilitic condition must be considered. Another possibility is that these apparent vegetations were only subendocardial hemorrhages on the edges of the valve leaflets—a condition described at length in the literature but not observed in any cases in this series.

Another baby living only two days and showing a marked jaundice after birth, presented at necropsy a definite abscess of the liver and acute splenitis. Since such a condition probably could not have developed in two days, this points strongly toward a hematogenous infection from the mother, who must have had at least a transitory bacteremia.

TABLE 6.—CONGENITAL SYPHILIS

		Per Cent.
A. Findings		
Associated with hemorrhagic disease........	5	
Associated with cerebral hemorrhage	3	
Associated with bronchopneumonia	1	
Alone	11	
Total	19	9½
B. Viability		
Living	11	
Dead	8	
Macerated, 2.		
Total	19	9½
C. History		
With history in parents	13	
Without history	6	
Total	19	9½
History in other cases without findings. 8.		
Body macerated without syphilis, 9.		

TABLE 7.—ACUTE INFECTIONS

Bronchopneumonia	4
Infected umbilical stump	1
Endocarditis (mitral and tricuspid).....................................	1
Abscess of liver with splenitis and hepatitis...........................	1
Total	7

A fourth baby showing evidences of congenital syphilis presented also a bronchopneumonia which did not at all resemble the "white" or syphilitic pneumonia. This child had lived seven days and, undoubtedly with a lowered resistance due to the syphilitic condition, early fell a prey to bacterial infection of the respiratory tract.

One case of especial interest was that of a full term infant who lived only two and one-half hours and presented at necropsy a very typical bronchopneumonia. Smears from the lung showed polymorphonuclear leukocytes and gram-positive cocci in pairs and chains. There is little doubt that this condition also developed in utero, although the mother appeared to be entirely normal. A fourth case of bronchopneumonia was found in an infant who lived three days and whose temperature reached 102 F. In this instance the mother, at the time

of delivery, was suffering from a severe attack of tonsillitis. These cases demonstrate very well the occurrence of infections contracted either in utero or at the time of birth.

Another infant apparently normal at birth, at three days of age developed a temperature of 105 F. and died the following day. The necropsy revealed a peculiar hemorrhagic process involving the greater part of both lungs. This picture was practically identical with the so-called "hemorrhagic bronchopneumonia" seen so frequently in patients dying of influenza. Since this occurred at the early outbreak of the 1918 influenza epidemic, it was probably an instance of this disease in a new-born infant—an uncommonly rare occurrence.

Another case of interest as an example of acute infection in the new-born has already been reported by Barron [5] but was excluded from this series because the infant lived eleven days. This was a case of cerebrospinal meningitis caused by a strain of *B. coli*.

TABLE 8.—SUMMARY

		Per Cent.
Cases examined	200	
Complete	136	
Traumatic deaths	15	7½
Cerebral hemorrhage	53	44
Hemorrhagic disease	41	20½
Malformations	30	15
Birth injuries	7	3½
Congenital syphilis	19	9½
Acute infections	7	3½

It would be of interest in this series, especially in those mothers showing no evidence of disease, to know how long before delivery the rupture of the fetal membrane took place. Early rupture of the membranes, as well as vaginal examinations, suggest a possible etiology for infections present in the infant at the time of birth.

In two cases only of the series did the cranial bones show ossification with practical obliteration of the fontanels. Partial atelectasis of the lungs seemed to be a common finding even in infants breathing spontaneously, but in three babies living for some time it was very marked and constituted the only lesion found. In these particular infants there must have been some as yet unrecognized factor preventing the normal expansion of the lungs and causing death by improper aeration.

Small hemorrhages under the pleura and epicardium were so common in this series that they cannot usually be considered more than terminal phenomena. In the majority of the cases also the foramen ovale was incompletely closed and the ductus arteriosus was entirely or partially patent.

5. Barron: Meningitis in the New-Born and Early Infancy, Am. J. M. Sc. **156**:358, 1918.

Just as this survey proves most conclusively the importance of performing a necropsy on every dead infant, it also shows that in order to obtain results of definite and permanent value each necropsy should be performed by a trained examiner. In many cases the lesions found in a new-born infant differ very markedly from those of the adult, e.g., the frequent occurrence of hemorrhages of the brain or developmental anomalies, such as patent foramen ovale and ductus arteriosus, etc. In the hands of an untrained observer such lesions as are often present in infants may either escape notice altogether or have placed on them undue significance in relation to the cause of death. Therefore, in order to obtain the most complete necropsies and to have uniformity in the reports, the specialization of one member of the pathologic staff in infant necropsies is most advisable. That such a member be also interested in the clinical field of pediatrics offers attractive possibilities. Such an arrangement has already been attempted at University of Minnesota, where a teaching fellow in pediatrics is also a member of the pathology staff. In addition to his clinical work he offers an elective in infant pathology, helps establish a branch museum of specimens from the new-born and also attempts to attend every postmortem examination on infants. Under such conditions these necropsies take on new significance and importance and stimulate the clinicians to greater activity in obtaining permissions and to greater interest, shown by attendance and frank discussion at the autopsy table. This interest is usually shared by pediatrician, obstetrician and pathologist, thus leading to a cooperation which renders possible an extension of medical knowledge in a field often neglected, and promotes that ideal of all medical work, the conservation of human life and health.

SUMMARY

1. Careful, complete, routine necropsies performed on all dead infants will return very valuable knowledge to the pediatrician, obstetrician and pathologist.

2. Cerebral hemorrhage is a common condition in new-born infants, occurring in from 43 to 50 per cent. of those examined.

3. Hemorrhagic disease of the new-born is also a frequent finding and is often associated with cerebral hemorrhage.

4. Malformations occurred in 15 per cent. of which only 4 per cent. were multiple. Of these, developmental defects of the heart were most common but those of the digestive tract were surprisingly numerous.

5. Birth injuries were rare (0.7 per cent.) but when they occurred they were usually in the spinal column.

6. Congenital syphilis is frequently diagnosed with difficulty, especially in the case of fetuses dead some time before birth.

7. Acute infections were rare; bronchopneumonia was the most frequent.

A CASE OF MENINGOCOCCUS MENINGITIS WITH OBSTRUCTIVE HYDROCEPHALUS IN THE NEWLY BORN *

J. HAROLD ROOT, M.D.

WATERBURY, CONN.

Although meningococcus meningitis is a common disease in later infancy and childhood, it is extremely rare during the first two months of life. In a careful review of the literature, I have been able to find reported only six cases of meningococcus meningitis occuring in infants under 2 months of age, only one of these having associated obstructive hydrocephalus. There are reported twenty-eight cases of meningitis due to organisms other than the meningococcus occurring in infants under 2 months of age. The causative organisms, and ages are shown in Table 1.

TABLE 1.—Analysis of Meningitis Cases as to Causative Organisms and Ages of Patients

Organism	Age	Total
Colon bacillus....................	Newly born (3); 3 days; 8 days; 9 days; 11 days; 16 days; 4 weeks (2); 6 weeks.......................	11
Staphylococcus and streptococcus	Newly born (6); 6 weeks (2); 7 weeks..............	9
Meningococcus....................	Newly born; 2 weeks; 29 days; 5 weeks; 6 weeks; 2 months...	6
Pneumococcus....................	Newly born; 3 days; 3 weeks; 8 weeks.............	4
B. lactic aerogenes................	8 days..	1
B. mucosus capsulatis.............	6 days..	1
B. pyocyaneus.......	8 days..	1
Micrococcus catarrhalis...........	39 days...	1
Total......................	....	34

REVIEW OF LITERATURE

Meningococcus Cases.—Holt,[1] in a discussion of 300 cases of meningitis in infancy and childhood mentions one case of meningococcus meningitis in an infant 5 weeks of age. This patient died of marasmus after all acute symptoms had subsided.

Koplik,[2] in an article on meningitis in the newly-born and infants up to 3 months of age, reports two cases. One of the two patients, in the newly-born, was cured of the acute symptoms. This patient later developed a moderate hydrocephalus. The second patient, aged 6 weeks, died after an illness of one week.

Miller[3] reports a case of meningococcus meningitis in an infant aged about 2 weeks. The infant died on the fortieth day. In this case the symptoms of

---

1. Holt, L. E.: Observations on Three Hundred Cases of Acute Meningitis in Infancy and Childhood, Am. J. Dis. Child. **1**:26 (Jan.) 1911.

2. Koplik: Meningitis in New-Born and Infants Under Three Months of Age, Arch. Pediat. **33**:481, 1916.

3. Miller, D. J.: Case of Meningococcus Meningitis in New-Born with Interesting Unusual Features, Arch. Pediat. **34**:824, 1917.

meningitis were not at all definite until a few days before death. Necropsy showed suppurative meningitis more marked over the sulci and at the base than elsewhere over the brain.

White[4] cites one case in an infant, aged 29 days. Repeated lumbar puncture produced only a few drops of fluid at times, none at other times; therefore, the diagnosis of acute hydrocephalus with obstruction was made. The infant was treated with intraventricular injections of serum, 180 c.c. in all being given. The infant recovered from the acute illness and died at 11 months showing an extreme hydrocephalus.

Haushalter and Remy,[5] in reporting a series of 272 cases of meningitis, mention one case of meningococcus meningitis in an infant aged 2 months. No particulars about the case were given.

Cases of Meningitis Other Than Those Caused by the Meningococcus.— Sherer[6] reports three cases of meningitis in infants aged 8 days, 9 days and 6 weeks, respectively. Necropsy in all three cases showed fibrinopurulent meningitis with bilateral otitis media, the organism in each case being the colon bacillus.

Hinsdale[7] describes a case of meningitis in an infant 3 days old, caused by *B. coli immobilis.* Necropsy showed a brain abscess in the left frontal lobe with exudate on the surface. He states that at birth pus came from the uterus of the mother during and after expulsion of the placenta.

Shieb[8] reports a case in an infant 8 days old caused by *B. lactis aerogenes* The diagnosis was made at necropsy, which showed a purulent meningitis.

Goldreich[9] records a case of antenatal infection with colon bacillus. The patient showed symptoms of meningitis on the first day of life, and died on the second. Necropsy revealed purulent meningitis, pleuritis and bronchitis.

Benfey[10] reports a case of *B. pyocyaneus* meningitis in an infant, aged 7 days. The patient died on the eighth day. There was an inflammation of the umbilicus.

Noeggerath[11] reports a case in a 16 days old infant caused by *B. coli immobilis capsulatus.*

Holt[1] also speaks of two cases of coli meningitis in infants 4 weeks old, and six cases of staphylococcus and streptococcus meningitis in the newly-born.

Bonhoff and Esch[12] report a case in an infant, 6 days old dying on the fourteenth day, due to *B. mucosus capsulatus.* Necropsy showed pus over the brain and an otitis media of the right side.

Michael[13] cites a case of colon meningitis in the new-born reported by Von Reus, no reference being given in his bibliography.

4. White, T. W.: Infectious Meningitis Developing in Babies from Twenty-Nine to Thirty Days Old. Case Reports, Arch. Pediat, **34**:372, 1917.

5. Haushalter and Remy, A.: Statistique dés meningites observées á la Clinique des Enfants d'un mois à 12 ans, Rev. méd. de l'est. **45**:533, 1913.

6. Sherer: Ein Beitrag zur Aetologie der Leptomeningitis Purulenta bei Säuglingen, Jahrsb. f. Kinderh. **39**:1, 1895.

7. Hinsdale: Purulent Encephalitis and Cerebral Abscess in New-Born Due to Infection from the Umbilicus, Am. J. M. Sc. **118**:280, 1899.

8. Schieb: Prag. med. Wchnschr., **5**:169, 1900.

9. Goldreich: Meningitis beim Neugeborenen, Jahr. f. Kinderh. **56**:808, 1902.

10. Benfey: Ueber Pyozyaneussepsis, Med. Klin. **50**:1199, 1907.

11. Noeggerath: Bacillus Coli Immobilis Capsulatus bei Einem Falle von Eitrigen Meningitis Cerebrospinalis, München. med. Wchnschr. **54**:617, 1907.

12. Bonhoff and Esch: Ueber Einem Fall von Meningitis purulenta beim Neugebornen infolge rechtseitiger Mittleohrentzündung, Ztschr. f. Geburtsh. u. Gynäk., **70**:886, 1912.

13. Michael: Recovery of Colon Bacillus from Spinal Fluid of Five Months Infant, Arch. Pediat. **33**:280, 1916.

Herman [14] reports a case of pneumococcus meningitis in an infant, aged about 3 weeks, saying that his case is the first one reported up to 1915. The infant died without symptoms of meningitis. Necropsy showed a thick yellow exudate on the anterior surface of the brain, and increased ventricular fluid.

Koplik [2] also reports three cases of streptococcus meningitis in infants aged 6 weeks (two cases), and 7 weeks (one case); one case of colon bacillus meningitis in a new-born; and two cases of pneumococcus meningitis, one an infant aged 8 weeks, and one in the new-born.

White,[4] in addition to the case already cited, reports a case in an infant aged 39 days, due either to the meningococcus or the *Micrococcus catarrhalis*. The infant died after an illness of thirty days. Necropsy showed dilated ventricles with membranous exudate.

Barron [15] finds in a review of the literature only thirty-nine cases of meningitis in infants under 3 months of age, nineteen of these being in the new-born. He adds one case of his own in an infant, aged 11 days, due to the colon bacillus. Necropsy showed fibrinopurulent exudate over the brain.

L'Esperance [16] reports a case of pneumococcus meningitis in an infant, aged 3 days. The baby died on the sixth day.

In the cases here reviewed, obstructive hydrocephalus was observed during the acute disease in ony one case. All of the cases, other than those due to the meningococcus, ended fatally, while of the six meningococcus cases, two patients died during the acute stage of the disease; one died later as a result of the development of hydrocephalus; one died of marasmus after all symptoms of meningitis had subsided; one recovered with a moderate degree of stationary hydrocephalus, and in one case the termination of the disease was not mentioned. The symptoms were at first obscure in the majority of cases, and indeed, the diagnosis was made only at the necropsy in several instances.

The findings in the following case seen in Dr. Howland's service at The Harriet Lane Home illustrates meningococcus meningitis with obstructive hydrocephalus, discovered at the age of 5 weeks, probably acquired at birth, or shortly thereafter. Definite symptoms were first observed at the age of about 2 weeks, but so obscure were these symptoms that it was not thought necessary for a physician to see the infant until he was almost 5 weeks old.

REPORT OF CASE

Baby C., a male infant, aged 5 weeks, was admitted to The Harriet Lane Home, May 22, 1919.

Family History.—Mother living, aged 22 years; has had almost constant indigestion and been very nervous since child's birth, otherwise well. Father, living and well, aged 25 years. There were no stillbirths or miscarriages. No

14. Herman, C.: Meningitis in New-Born with Report of a Case, Arch. Pediat. **33**:384, 1915.

15. Barron, M.: Meningitis in New-Born and Early Infancy, Am. J. M. Sc. **156**:358, 1918.

16. L'Esperance: Meningitis in an Infant Six Days Old, Med. Rec. **97**:548, 1920.

children have died. Patient, second child; one other, a girl 3 years old, living and well. No history of syphilis. There was a possibility of tuberculosis in paternal grandmother.

Previous History.—Born at full term, normal delivery; birth weight 7 pounds. Appeared to be a normal healthy baby at birth. No jaundice, hemorrhages, snuffles or convulsions at birth. Was breast fed eleven days irregularly, then because of nervousness of mother, green stools, fretfulness, and irritability of baby was put on a condensed milk mixture. Did not do well on this, so was again placed on breast, to be changed again to condensed milk because of vomiting and failure to gain in weight.

Present Illness.—Since birth the infant appeared to be very nervous, twitching at slightest provocation; was also very irritable. He had always cried a great deal. Shortly after birth, the parents thought they noticed slight retraction of the head, although they were rather indefinite as to when they were sure of this condition. They also thought the fontanel had always been full. At the age of 10 days, a diffuse mottled rash appeared, lasting two days, which the parents took to be measles. At this time also the baby began to spit up some of his food, and thrush was noticed, which persisted for some time. Occasional attacks of fever then began, and the retraction of the head and tense fontanel were said to be definite. From then until the infant was 33 days old, the same symptoms existed, only growing steadily worse. The first real convulsion occurred on the thirty-third day, and vomiting became quite pronounced. Convulsions and vomiting were persistent from then until admission to the hospital four days later.

Physical Examination.—Measurements: Head, 37.5 cm.; chest 31 cm.; abdomen, 30 cm.; length, 42 cm. The general appearance is that of a poorly nourished and developed and apathetic appearing white boy, lying quietly in bed when not undergoing a convulsion or twitching. He cannot be made to cry, but at the slightest movement twitching occurs. The skin shows occasional petechiae on the body and extremities. The head is large symmetrical; fontanels are both wide open and bulging. The sutures are separated. No craniotabes. The eyes are rolled upward with each convulsion, but between times show occasional vertical nystagmus. No strabismus. Pupils are equal, regular in outline, and react to light. Conjunctivae are slightly injected. Sclerae are clear. There is a slight purulent discharge from both eyes. The ears show no secretion or mastoid tenderness. There is a mucopurulent secretion from both nostrils, no obstruction. Tongue is slightly red, with whitish coat, moist. Tonsils and pharynx are slightly injected. Respirations are rapid. Lungs show no impairment of resonance. Breath sounds are normal. The liver and spleen are both barely palpable. The knee jerks are equal and lively; no Babinski; Kernig questionable on both sides, biceps and triceps present and equal. Superficial reflexes not obtained. There is marked rigidity of the neck. The external genitalia are normal. Otoscopic examination shows both ear drums normal. Ophthalmoscopic examination shows a choked disk on both sides.

Laboratory Examination. — White blood count, 18,000. Von Pirquet test negative. Urine shows slightest possible trace of albumin, no sugar; sediment shows amorphous urates only.

A lumbar puncture done on admission yielded 4 c.c. of brownish cloudy fluid, obtained drop by drop, with difficulty. The fluid showed positive globulin (Pandy), many leukocytes, the majority being polymorphonuclears, with also a considerable number of endothelial cells. No organisms were found in smears from this fluid, and cultures were all negative. A ventricular puncture done at this time yielded cloudy fluid under increased pressure. Twenty c.c. were removed from the right ventricle and 10 c.c. of serum were introduced. A smear from this fluid showed many cells, mostly polymorphonuclears, with an abundance of gram-negative intracellular and extracellular diplococci. Cultures showed the meningococcus.

Clinical Course.—May 23: Temperature, 103 F.; pulse, 160; respiration, 52. The infant appeared slightly better. Convulsions had ceased, although twitching of the lips and hands continued. Took feedings well; no vomiting. Temperature and pulse higher than on the previous day. A ventricular puncture was done in the morning, 45 c.c. of fluid being removed and 40 c.c. of serum given. A lumbar puncture done in the afternoon gave identical results as on the previous day, also 10 c.c. of serum were introduced this time. The infant showed no ill effects from the punctures. Another ventricular puncture was done at 10 p. m., in the left ventricle, 45 c.c. of fluid being removed and 20 c.c. of serum introduced. The number of organisms seen in smears from this fluid was greatly diminished and cultures gave scanty growth. The patient became slightly cyanotic after this puncture and vomited. The reaction lasted only a few minutes, however. Temperature rose to 106 F. two hours after the puncture, falling again in the following two hours to 102 F.

May 24. Temperature, 103 F.; condition about the same as on the previous day. A lumbar and ventricular puncture were done in the afternoon. Only 4 c.c. were again obtained by lumbar puncture. Forty c.c. of fluid were withdrawn from the ventricle, and 20 c.c. of serum introduced. In both fluids the cell count was lower and no organisms were seen in smears, or grew in cultures this time. The ventricular puncture was again followed by cyanosis and slowing respirations, but improvement occurred shortly after a stimulant was given. The improvement was, however, only temporary, the infant again becoming cyanotic, twitching almost continually, and respirations growing slower until they ceased an hour later. Permission for necropsy was refused.

DISCUSSION

The obscurity and irregularity of the symptoms in meningitis of the new-born in the early stage of the disease is admitted by all observers. The most constant symptoms are vomiting (not projectile), extreme restlessness, twitching, (general), convulsions (repeated), later, bulging of the fontanel and retraction of the neck.

Miller's case illustrates this course. The onset was at 2 weeks of age with conjunctivitis and a vesicular eruption on the abdomen. The first definite symptom of meningitis (tremor of the eyelid), occurred at twenty-five days, followed by convulsions and other typical symptoms of meningitis. The infant died ten days later.

Holt and Koplik both remark on the irregularity in the clinical course. Koplik found the temperature high at onset, going to normal or 1 degree above later in the disease. Convulsions, frequently repeated, twitching, restlessness, vomiting and groaning respirations are important symptoms. He found that after a week or more, rigidity of the neck, and bulging fontanel develop. He thinks that tetany and meningeal hemorrhage are two conditions most often confused with miningitis. Tetany, however, occurs in later infancy (from 6 months to 2 years). In the cases of meningeal hemorrhage, there is no fever, convulsions are not repeated, the fontanel has a boardlike feel with no pulsation, and does not become prominent as the disease progresses.

In the case here reported, the infant was not seen until the symptoms were quite definite. He showed at this time a temperature of

103 F., frequent convulsions, twitching, vomiting (not projectile), bulging fontanel, retracted neck, very large head with separated sutures, and questionable Kernig. The parents stated that he had been restless and irritable since birth. The first symptom was a mottled rash at the age of 10 days. This was followed in a few days by thrush, and from then on occasional attacks of fever. At 2 weeks of age, slight retraction of the head was definitely noted, and vomiting began at this time. The vomiting was not severe, however, until the infant was 4½ weeks old. The first convulsion occurred on the thirty-third day, and the child was brought to the hospital on the thirty-fifth day. The fact that the head was so large in size with separated sutures, that there was a choked disc on both sides, but especially that only a few drops of fluid were obtained on lumbar puncture, while a large quantity was obtained on ventricular puncture, establishes the diagnosis of obstructive hydrocephalus associated with the meningitis.

SUMMARY

Meningococus meningitis in the new-born and early infancy is rare. Only one case of meningococcus meningitis with obstructive hydrocephalus developing during the acute stage of the disease was found in the literature.

The symptoms are usually irregular and obscure. The most important ones are repeated convulsions, vomiting (not projectile), and after a week or more, bulging of the fontanel and rigidity of the neck.

PROGRESS IN PEDIATRICS

REVIEW OF THE EAR, NOSE AND THROAT LITERATURE FOR THE YEAR 1919 *

G. W. BOOT, M.D.
CHICAGO

As might have been expected, the literature for 1919 is full of articles of a military nature having but little bearing on the work of a pediatrician. In addition to this most of the foreign journals have not found their way to this country.

THE EAR

Dean and Bunch [1] have constructed a pitch range audiometer driven by electricity that covers the range of hearing in ordinary use without a break, enabling one to test out the hearing very rapidly. Both the pitch and the intensity of the tone are under perfect control.

In an article on teaching the deaf child, Goldstein [2] states that more than 2,000 children were attending the public schools of St. Louis, who had some form of speech defect, many of these, no doubt, being the result of defective hearing.

Heilshon observed three patients who had lost their hearing from mumps.

Blackwell [3] divides earache into four classes: (1) Inflammation behind the tympanic membrane, usually preceded by inflammation in the upper air passages; (2) inflammation of the soft parts of the external auditory canal; (3) otalgia, the pain being referred from teeth, nose or throat, and (4) mechanical, occurring mainly in children with enlarged tonsils and adenoids. The pain in this form is nearly always nocturnal.

COMPLICATIONS OF EAR DISEASE

Holmes [4] seems to think that mastoiditis is the same as an abscess anywhere, and that opening is indicated as soon as pus is formed. He says, "It is, therefore, a self evident proposition that to operate at the earliest possible moment is sound surgery and should always be followed." (I believe that most otologists will disagree with this

statement for pus is found in the mastoid in practically every case of acute suppurative otitis media, and if every patient with pus in the mastoid is operated on, it would mean operation for practically every case of acute suppurative otitis media, and since the great majority of cases of acute suppurative otitis media recover without operation, many needless operations would be done if this advice were followed).

Kernan[5] gives the history of a child, aged 5 years, who probably had had influenza three weeks previously, recovering in ten days. Eight days later he became feverish, vomiting on the ninth day. Two days later he entered the hospital with practically negative symptoms. A few days later his neck became rigid with a doubtful Kernig. He was irritable, hyperesthetic, and would not answer questions. He next developed convulsions, nystagmus and left facial paralysis. A mastoid operation was done on the left mastoid and the cerebellum explored. Gas escaped from the wound but no pus was found. The final outcome of the case is not given. In a case reported by Mann,[6] the patient had a right sided cerebellar abscess. When the patient's nose was held, he always used his left hand to brush away the hand holding his nose.

Mollison[7] reports the case of a boy, aged 12½ years, who had scarlet fever at 2. He had a right frontal headache, vomiting, tenderness over the right mastoid and was supposed to have had mumps two weeks previously. His temperature was 97 F., pulse 68. He was drowsy and had photophobia. There was pus in the right ear. A mastoid operation was done on the right side, the right temporosphenoidal lobe was explored and one ounce of pus evacuated. He improved, but the pus reaccumulated and had to be evacuated a second time, following which a hernia cerebri developed. A large part of the hernia was pulled off and was found to consist of the abscess sac. Ophthalmoplegia developed three days later. The patient made a slow but complete recovery.

Borries[8] finds that the cerebrospinal fluid may be sterile, particularly in cases in which the meningitis is an accompaniment of pachymeningitis interna or brain abscess.

Aboulkir[9] classifies meningitis as follows:

(1) Purulent septic meningitis; (2) purulent aseptic meningitis; (3) serous septic meningitis; (4) serous aseptic meningitis, presenting itself under two forms, diffuse and hypertensive. He reports the following cures: Septic meningitis, one patient cured by medical

5. Laryngoscope **29**:322, 1919.
6. Ztschr. f. Ohrenh. **74**:4, 1919.
7. J. Laryngol., Rhinol. & Otol. **34**:161, 1919.
8. Arch. f. Ohrenh., Nasenh. u. Kehlkopfh. **103**:37, 1919.
9. Rev. de l'Or. et d. Rhin., (May 15) 1919.

treatment, one by mastoid operation, and one by mastoid operation with incision of the meninges. Aseptic meningitis—one patient cured spontaneously, six patients cured by mastoid operation, and four cured by mastoid operation with incision of meninges (once with puncture of the ventricle).

The same author [10] says that the classic treatment of intracranial complications of ear diseases is dominated by three principal considerations: (1) Difficulty of diagnosis; (2) necessity of early operation, and (3) necessity of opening the cranium and following osseous lesions and of traversing the mastoid in successive steps.

A number of interesting papers on mastoiditis appeared during the year, and a number of interesting points in the disease were brought out.

Harris,[11] in a paper on ear diseases following measles at Fort Oglethorpe, states that of 1,685 cases of ear disease treated at Fort Oglethorpe, 607 were the result of measles. Usually the ear trouble developed without complaint from the patient and was discovered during routine examination. The rule was to do a paracentesis as soon as any change was discovered in the membrana tympani. Acute mastoiditis appearing in a patient suffering from measles is usually as free from pain as is the otitis media. On account of the great gravity of the mastoid cases, operation was performed under gas-oxygen anesthesia. Of thirty-one patients so operated on, ten had bronchopneumonia and one had mumps. There were no complications and no shock following anesthesia.

Robinson [12] reported a case of toxic delirium following an operation for mastoiditis. The patient became insane with delusions of persecution.

Goldstein [13] reports a series of mastoid operations done under local anesthesia with the minimum of pain and maximum of safety and with 100 per cent. perfect recoveries. (This method of operation should be done more where the patient is very toxic as in scarlet fever, where nephritis is present, or where the patient has pulmonary lesions that may be aggravated by general anesthesia.

Haines [14] reported a case of mastoiditis in a hemophiliac on whom operation was done. It was necessary to do transfusion twice and to use coagulin Ciba. The patient recovered.

Smith [15] considers that mastoiditis occurring in patients with fracture of the skull has a very poor outlook because of the meningitis that is apt to occur. Tilley [16] claims that filling the mastoid wound

10. Rev. de l'Or. et d. Rhin., (March 15) 1919.
11. Ann. Otol., Rhinol. & Laryngol. 28:50, 1919.
12. Ann. Otol., Rhinol. & Laryngol. 28:86, 1919.
13. Laryngoscope 29:559, 1919.
14. Laryngoscope 29:609, 1919.
15. Laryngoscope 29:552, 1919.
16. Laryngol., Rhinol. & Otol. 34:73, 1919.

with a mixture of bismuth subnitrate, iodoform and liquid paraffin, and completely suturing the wound, materially shortens the after-treatment of mastoiditis.

Stickney [17] reported two cases of Gradenigo's syndrome in patients aged 6 and 34 years, respectively, both females. In the child an acute rhinitis was followed by acute suppurative otitis media on the left side and this by paralysis of the left abducens. A simple mastoid operation was done and the diplopia subsided inside of two weeks. In the second case it was necessary to introduce a drain between the dura and the bone almost to the apex of the petrous portion before improvement set in.

Hill [18] had a patient who had spontaneous hemorrhage after a simple mastoid operation. The patient recovered.

McKinley [19] had a case of spontaneous recovery from thrombosis of lateral sinus.

Inhope [20] considers that the patient's chances of recovery after an operation for sinus thrombosis may be put at 50 per cent.

Holmgren [21] uses radium in the treatment of tubal stenosis. Lymphoid tissue, in particular, is particularly susceptible to the influence of radium, and stenosis of the tuba is largely due to lymphoid tissue in its mucosa. His results were satisfactory.

Agazzi [22] says that tuberculosis of the ear does not always occur by way of the tuba, but that it also occurs by way of the circulation.

MOUTH AND THROAT

Canuyt [23] reports a case of noma and advises for treatment the use of stimulants and cardiac tonics, derivatives and intravenous injections of collargol, electrargol and camphorated water. For local treatment he advises caustics, combating local symptoms after separation of the slough. He finds noma rare in France but common in hot countries like Annam where it occurs after eruptive fevers, typhoid fever, pneumonia, diphtheria, etc. Poor nutrition, poor housing and insanitary conditions favor its development. It never occurs in the course of good health. He divides its course into three periods:

1. Invasion: Ulceration of inside of cheek or on gums, or a hard area of induration.

2. Period of progress: Ulceration progresses or multiplies and gangrene sets in. The skin becomes gangrenous in turn.

17. Laryngoscope **29**:90, 1919.
18. Ann. Otol., Rhinol. & Laryngol. **28**:566, 1919.
19. Laryngoscope **29**:13, 1919.
20. Arch. f. Ohrenh., Nasenh. u. Kehlkopfh. **103**:97, 1919.
21. Laryngoscope **29**:590, 1919.
22. Monatschr. f. Ohrenh. u. Laryngorhinol. **48**:676, 1919.
23. Rev. de Laryngol., Otol. et Rhinol. **40**:6, 1919.

3. Period of elimination and repair: Line of demarcation forms, sloughing occurs, to be followed by granulation and healing. In the differential diagnosis are to be considered gangrenous aphtha, ulcero-membranous stomatitis, malignant pustule and malignant syphilis.

Bryan [24] considers all local treatment of tonsils after cultures have shown the presence of *Streptococcus hemolyticus* as not only deceptive, but a waste of time. A complete enucleation is necessary.

Nichols [25] finds that carriers of streptococci are very common—in over half the population.

Moore [26] in an article on hemorrhage after tonsillectomy gives the following sources for the bleeding:

(1) Tonsillar artery; (2) ascending pharyngeal artery; (3) descending palatine artery; (4) ascending palatine artery; (5) dorsalis linguae artery; (6) capillary oozing; (7) enlarged venous plexus, and (8) internal carotid artery. The ascending palatine artery is in the anterior pillar. The descending palatine artery is in the posterior pillar. The tonsillar artery is in the posterior pillar as is also the pharyngeal artery. He advises that tonsillectomy should be deferred if inflammation is present, and cautions against pernicious anemia, leukemia, albuminuria and the menstrual period. Operation is contraindicated in hemophilia and purpura. The amount of hemorrhage at the time of operation depends on the skill of the operator. Ligature of the common carotid is not recommended but suture of the pillars is.

Baum [27] says that a clot should never be left in a bleeding tonsillar fossa. He prefers ether for anesthesia, the pharyngeal reflex being abolished but the laryngeal being retained. Novocain is a satisfactory local anesthetic, but cocain is dangerous and sloughing has followed the use of quinin and urea hydrochlorid. "There is no doubt that deaths have occurred from status lymphaticus." (Just as they formerly occurred from "heart failure"—in other words, from an unknown cause.) Acidosis often occurs but is not serious, as a rule. Sepsis occasionally occurs. Pulmonary abscess after tonsillectomy occurs in two different ways; by aspiration of blood and by infection through the circulation, either venous or lymphatic. (A septic thrombus forms in the venous plexus around the tonsil and the lung abscess results from an embolus detached from this thrombus.)

Dabney [28] reports four cases of delayed secondary hemorrhage occurring after tonsillectomy in the course of twelve years' work. One occurred ten days after tonsillectomy. Two patients were operated on under local anesthesia and two under general. The hemorrhage apparently was the result of separation of a slough.

24. Ann. Otol., Rhinol. & Laryngol. **28**:337, 1919.
25. Ann. Otol., Rhinol. & Laryngol. **28**:344, 1919.
26. Texas State J. M. **14**:300 (Jan.) 1919.
27. Ann. Otol., Rhinol. & Laryngol. **28**:37, 1919.
28. Kentucky M. J. **17**:204 (May) 1919.

Lillie and Lyons [29] say that: (1) Tonsillectomy is justified in every frank case of myositis or arthritis; (2) a marked improvement occurs in 79 per cent. of such cases from tonsillectomy alone; (3) all dental sepsis should be removed, and (4) the size of the tonsil has no bearing on its possibilities for infection.

Albert and Douglass [30] state that bone or cartilage has been found in the tonsils in the following forms: (1) Elongation of hyoid or styloid process, and (2) bony plates or nodules or cartilaginous nodules.

LaMotte [31] reports a case of styloid process appearing in the throat along the left anterior pillar as a glistening surface that felt hard. The tonsils were removed and a piece of the process three-fourths of an inch long dissected out with great relief to the symptoms. (Such cases are apt to present great difficulties to the man who does tonsillectomies, unless he is sufficiently familiar with the literature to recognize the condition.)

Taylor [32] is convinced that septic tonsils and enlarged infected adenoids are an important factor in the etiology of recurrent vomiting; of twenty-one cases operated on, only one was unimproved after removal of tonsils and adenoids.

Milne [33] reports two cases of phlyctenular disease that cleared up promptly on removal of adenoids. He finds that over 80 per cent. of children with enlarged glands have adenoids.

Baum [34] states that in the bleeding of hemophiliacs after tonsil and adenoid operations, transfusion is the remedy of choice. Adenoid bleeding is scarcely serious. Otitis media may follow tonsil and adenoid operations. The same author finds that acidosis occurs more often after tonsil and adenoid operations than in any other one class of patients but that it is not serious as a rule. He advises pre-operative and postoperative examination of the urine for acetone and diacetic acid, with administration of sodium bicarbonate and glucose as measures of safety.

Bane [35] reports the case of a boy, aged 13, in whom a peritonsillar abscess was diagnosed, but on incision nothing was found. A gland was removed for diagnosis and the growth found to be a large cell sarcoma. Radium gave considerable temporary improvement, but the patient died a few weeks later.

Dean [36] believes that not only all tuberculous retropharyngeal abscesses, but all other abscesses should be opened externally. For

29. J. A. M. A. **72**:1214 (April 26) 1919.
30. Ann. Otol., Rhinol. & Laryngol. **26**:909, 1919.
31. Laryngoscope **29**:288, 1919.
32. Minnesota M. J. **2**:61 (Feb.) 1919.
33. Brit. J. Ophth. **3**:163, 1919.
34. Ann. Otol., Rhinol. & Laryngol. **28**:37, 1919.
35. Ann. Otol., Rhinol. & Laryngol. **28**:828, 1919.
36. Ann. Otol., Rhinol. & Laryngol. **28**:566, 1919.

this purpose he makes an incision just in front of the sternocleido-mastoid muscle, with the lower end opposite the cricoid. The vascular sheath of the carotid is exposed and the finger inserted between the vascular sheath and the visceral fascia and passed down to the retro-pharyngeal space. The operation is simple, requires but a few minutes and should be almost without shock.

Brown [37] states that 96 per cent. of cases of acute retropharyngeal abscesses occur in children under 6 years of age, and 50 per cent. between the ages of 6 and 12 months.

Mosher [38] had a patient develop thrombosis of the internal jugular and pyemia as a result of retropharyngeal abscess.

Jewell [39] had a female patient, aged 13, with nasal voice, lumps in the throat and intermittent headache and earache. The growth which was attached to the left lateral and posterior wall of the postnasal space bled readily. The lymph glands on the left side of the neck were enlarged. Later, vomiting and blindness, first of the left eye and then of the right, developed, followed by coma and death. The growth was found to be endothelioma.

Ray [40] reports a case of sarcoma of the nasopharynx that was treated by radium. It improved at first but the patient died two months later.

White [41] observed a girl, aged 13, with a large fibroma of the nasopharynx.

Patterson [42] reports a case of fibroma of the nasopharynx in a boy, aged 18. Symptoms had been present for two years. They were: obstruction of the left naris, change in speech, pain in the left cheek, pain over the right eye, firm swelling in the temporal region, below the zygoma and in the nasopharynx.

Barroud [43] reports a case of complete bony atresia of both choanae in a baby aged 3 days. The symptoms were inability to drink and a profuse discharge from each nostril. He drilled a hole 4 mm. in diameter through each choana and passed a rubber tube into one hole and out of the other. The child now drinks freely with no disturbance of breathing and has increased considerably in weight.

St. Clair Thompson [44] reports the case of a female infant, aged 4 weeks, in whom there were three good sized vestibules to the nose with two columellae. The two external nostrils were true nostrils. The two false nostrils were culdesacs ¼ and ½ inch long.

37. Laryngoscope **29**:638, 1919.
38. Laryngoscope **28**:638, 1919.
39. J. Laryngol., Rhinol. & Otol. **34**:306, 1919.
40. Laryngoscope **29**:602, 1919.
41. Laryngoscope **29**:499, 1919.
42. J. Laryngol., Rhinol. & Otol. **34**:306, 1919.
43. Arch. f. Ohren-Nasen- u. Kehlkopfh. **103**: (Abst.) 4, 1919.
44. J. Laryngol., Rhinol. & Otol. **34**:207, 1919.

Dean and Armstrong [45] found nasal sinus diseases as a cause of multiple arthritis in children. They also found sinus infection to blame for repeated colds after slight cause, for a case of noma, for cyclic vomiting, for asthenia, etc. Methods of diagnosis of accessory sinus disease in children are very unsatisfactory and great patience and persistence are necessary to arrive at definite conclusions. The most common symptoms were sneezing, recurrent stopping of the nose, frequent colds, nasal discharge, headache, poor appetite, poor color, etc. Direct examination of the nose was unsatisfactory. The nasopharyngo-scope was a great help. Roentgen-ray examination is very necessary to determine the size of the sinuses, but not much help in learning their pathologic condition. Their treatment was first to remove adenoids and tonsils, and if this did not relieve the trouble to open the maxillary sinus in the lower meatus.

Albright [46] says there is no doubt that most cases of migraine are caused by accessory sinus disease.

Vail [47] reports four cases of orbital abscess due to intranasal suppuration. One patient had exophthalmos of the right eye and thrombosis of the cavernous sinus from sphenoidal suppuration. Another patient had exophthalmos from abscess of the posterior ethmoid cells. The globe was pushed straight forward. The third patient had abscess of the anterior ethmoids and the globe was pushed forward and toward the temple. The fourth patient had abscess of the frontal sinus. The globe was extruded to a less extent and was pushed downward. In all four cases the exophthalmos was on the right side. The first and third patients died. The second patient recovered. The fourth patient disappeared from view. Vail had six recoveries out of seven cases, before the days of modern ethmoid operations. In these he did external operations. One patient died from brain abscess. Six of these cases occurred in young adolescents who developed abscesses as a result of tonsillitis, measles and scarlet fever.

Wood [48] had a case of osteomyelitis of the frontal bone following frontal sinusitis. He considers such conditions as more common after acute frontal sinusitis than after the chronic form. (In my experience such conditions are more commonly the result of tertiary syphilis.)

Benian and Hayton [49] consider the causative organisms of ozena to be the *Bacillus capsulatus* of Lowenburg, the acid-fast bacillus of

45. Ann. Otol., Rhinol. & Laryngol. **28**:452, 1919.
46. Journal-Lancet **39**:490, 1919.
47. Laryngoscope **29**:263, 1919.
48. Laryngoscope **29**:612, 1919.
49. J. Laryngol., Rhinol. & Otol. **34**:325, 1919.

McKenzie and Wingrave and the cocco-bacillus of Perez. They apply glycerin or glucose to the nose, painting it from one to six times daily, and advise against douching.

Erzner,[50] reporting on vaccine and serum therapy of ozena, says: "It is most discouraging that this work should all be negative."

Unger [51] presented a case of leprosy where the first lesions were in the nasal mucosa, which showed three little tubercles. Diagnosis was confirmed by both sections and smears..

Rose [52] reports a case of round cell sarcoma of the antrum in a boy, aged 15. He has treated three such cases in children, one aged 4, one 12 and one 15. Shattuck in the discussion warns against errors of laboratory diagnosis in such cases.

LARYNX, TRACHEA, BRONCHI AND ESOPHAGUS

Albrecht [53] demonstrated sections of the larynx showing both tubercle bacilli and *Spirochaeta pallida*.

Denker [54] states that trauma of the larynx may result in death from hemorrhage, asphyxia or by mediastinal abscess. The larynx is protected from injury by its position under the chin, by its elasticity and by its movability.

Myers [55] reports a case of hoarseness due to paresis of the thyro-arytenoideus internus caused by suction used in treatment of the accessory sinuses.

Jackson [56] believes that closing the opening in the tracheotomy tube as far as possible without danger to the patient develops the laryngeal muscles and tends to prevent and to cure laryngeal stenosis.

Faulkner [57] reports a case with paralysis of the left vocal cord, associated with paresis of the sternocleidomastoid, trapezius, tongue, omohyoid and left arm. The lesion must have been in the cord, probably above the second and third cervical vertebrae.

White [58] observed a case of syphilitic laryngitis in a child of 7. The epiglottis was swollen and ulcerated, the swelling extending down into the larynx and hiding the cords.

Hill [59] advises radium in the treatment of papilloma of the larynx.

50. Laryngoscope **29**:21, 1919.
51. Laryngoscope **29**:316, 1919.
52. Laryngoscope **29**:176, 1919.
53. Arch. f. Ohren-Nasen- u. Kehlkopfh. **103**: (Abst.) 24, 1919.
54. Laryngoscope **29**:60, 1919.
55. Laryngoscope **29**:720, 1919.
56. Laryngoscope **29**:16, 1919.
57. Laryngoscope **29**:60, 1919.
58. Laryngoscope **29**:500, 1919.
59. J. Laryngol., Rhinol. & Otol. **34**:250, 1919.

Grant [60] removed a papilloma of the larynx in a boy 4 years of age under suspension laryngoscopy.

Tod [61] had a patient, aged 4 years, die five weeks after tracheotomy and excision of a laryngeal papilloma. The postmortem examination showed false membrane in the larynx, trachea and bronchi. Purulent bronchitis was present. Smears gave streptococci and bacilli which did not resemble diphtheria.

Jackson [62] says that metallic foreign bodies, glass, pebbles and vulcanite cause very little reaction in the bronchi. Soft rubber is more irritating and vegetable substances, such as beans, peas, maize and peanuts, give a very violent reaction which is generally fatal if left alone. Roasted peanuts give the most violent reaction. Most foreign bodies tend to migrate downward towards the periphery. When the foreign body becomes fixed, a septic cavity results. Foreign bodies are more common in the right bronchus than in the left. In cases in which a foreign body has been retained a long time, clinical signs of tuberculosis result. In old cases the pus is very foul, dark and abundant. In peanut cases the pus is pink in color. Subglottic edema is apt to result in children under 19 months.

St. Clair Thompson [63] reports the case of a girl, aged 10, who had teeth extracted. Four weeks later a foreign body in the lung was suspected because of wheezing, cough, etc. Roentgen-ray examination showed a tooth in the lung. Direct bronchoscopy under chloroform was done for forty-five minutes without results. A month later, lower bronchoscopy was done under chloroform and was successful. Recovery was uneventful. He also reports a case of collar button in the right bronchus of a child, producing collapse of the lung of one year's duration. (I have had a collar button in the left bronchus two years.)

Rosier [64] reports a tooth plate in the trachea of a soldier for four months. He had received a wound and was operated on, under chloroform. On awakening he noticed the absence of a left upper tooth, but was told it had fallen on the floor and was lost. Three days later he was evacuated after being examined by the medecin major who found nothing but a few râles of bronchitis. Some months later he was gassed. He ate and slept perfectly, but three or four times during the day and night he had violent coughing spells. He was examined laryngoscopically and laryngitis was diagnosed. Four months after his first operation he was examined and a foreign body found in the trachea. Under cocain anesthesia it was removed. Prompt recovery followed.

---

60. Ibid.
61. J. Laryngol., Rhinol. & Otol. **34**:254, 1919.
62. J. A. M. A. **73**:672 (Aug. 30) 1919.
63. J. Laryngol., Rhinol. & Otol. **34**:361, 1919.
64. Rev. de Laryngol., Otol. et Rhinol., (April 30), 1919.

Barthes [65] reports the removal of a live leech from the larynx.

St. Clair Thompson [66] uses his report of a tooth impacted in the bronchus as a text for giving the advantages of lower bronchoscopy over upper bronchoscopy, e. g.: (1) Less trouble with the anesthetic; (2) fewer assistants needed; (3) use of shorter bronchoscopic tube; (4) better illumination; (5) larger field of vision; (6) greater facility of manipulation; (7) less leverage on lung; (8) shorter time required; (9) more certain results, and (10) greater security should the foreign body change position.

Arrowsmith,[67] in an article on the history of bronchoscopy, gives abstracts of 140 cases of foreign bodies in the bronchi and lungs before the days of bronchoscopy.

Schmieglow [68] calls attention to the possibility of suffocation from rupture of tuberculous lymph glands into a bronchus and reports a case where he made a diagnosis of such a condition.

Guthrie [69] says that the blind removal of foreign bodies from the esophagus is scarcely to be defended. He reports the case of a poorly nourished baby that had inhaled a fishbone. Upper bronchoscopy failed. Tracheotomy was necessary the same evening on account of edema of the larynx. Lower bronchoscopy next day also failed. The child died two days later of bronchopneumonia.

Digestion of the esophagus is a cause of postoperative hemorrhage.

Pringle and Teacher [70] have had eighteen cases, most of them abdominal cases. Vomiting begins soon after operation. The vomitus is acid and scalds the throat. The amount of blood vomited is small. Postmortem, numerous submucous hemorrhages, erosions and perforations of the esophagus were found with fibrinous exudate on the pleura opposite the esophagus. The submucous hemorrhages showed that the condition existed antemortem.

Oppikofer [71] says that foam in the pyriform sinus is a symptom very suggestive of diverticulum of the esophagus.

Thompson [72] had a girl, aged 15, who had a fusiform dilatation of the esophagus which was covered with *Oidium albicans.* Lavage with hydrogen peroxid and eusol relieved but did not cure the condition.

Farren [73] found fibroma of the esophagus in a boy, aged 10.

65. Rev. de Laryngol., Otol. et Rhinol. **40**:391, 1919.
66. Loc. cit.
67. Laryngoscope **29**:673, 1919.
68. Arch. f. Ohren-Nasen- u. Kehlkopfh. **103**: (Abst.) 65, 1919.
69. J. Laryngol., Rhinol. & Otol. **34**:38, 1919.
70. Brit. J. Surg. **6**:523, 1919.
71. Arch. f. Ohren-Nasen- u. Kehlkopfh. **103**: (Abst.) 62, 1919.
72. J. Laryngol., Rhinol. & Otol. **34**:101, 1919.
73. Arch. f. Ohren-Nasen-u. Kehlkopfh. **103**: (Abst.) 68, 1919.

Keiper [74] contributes an article on tight strictures of the esophagus due to burns. He recommends that no attempt be made at bougieing until two sets of roentgenograms have been made to locate accurately the site of the stricture. No bougies should be passed, except under direct inspection through the esophagoscope. Blind bougieing is dangerous. Frequent anesthesia for bougieing is highly dangerous. The strictures caused by lye are often multiple and tortuous.

MISCELLANEOUS

Lake,[75] in an article on aural bacteremia, considers it a condition in which living bacteria are present in the blood stream. It is to be distinguished from pyemia, in which there is only occasional entry of bacteria into the blood stream. The presence of bacteria is indicated by the temperature. Bacteria are found in greatest numbers during the time when the temperature is rising. They diminish in number when the temperature falls. "In those conditions in which they are constantly present the temperature never falls very low." Such cases, as well as the cases in which the temperature rises and falls excessively, are apt to end fatally. Rigors are not present in bacteremia. The temperature remains between 100 and 104 F. These seems to be cerebral stimulation, and the patient's mental processes are unusually quick. The prognosis is not bad. The treatment should be by: (1) autogenous vaccines; (2) blood antiseptics, such as hexamethylenamin in full doses, and (3) physiologic sodium chlorid solution subcutaneously.

Primary aural diphtheria has been seen in both sexes, according to Pugnat.[76] It attacks both adults and children, but is more common in children. It may appear before the nasal symptoms. Discharge from the ear should be examined bacteriologically.

Putawski [77] calls attention to dysphagia as a symptom of dilatation of the left ventricle.

Goldstein [78] concludes that epistaxis occurs as one of the earliest symptoms of "flu," that it seems to be invariably on the septal side of the naris and that cases in which epistaxis occurred were the most liable to develop complications. The *Streptococcus hemolyticus* was definitely established as the etiologic factor in the epistaxis. In sixty cases he used horse serum and had no fatalities.

Roy,[79] in an interesting article on syphilis among the blacks of Africa, dealing largely with the history of syphilis, mentions 135 cases in seventeen of which there were perforations of the septum, perfora-

74. Laryngoscope **29**:48, 1919.
75. J. Laryngol., Rhinol. & Otol. **34**:110, 1919.
76. Rev. de Laryngol., Rhinol. et Otol. **40**:377, 1919.
77. Arch. f. Ohren-Nasen- u. Kehlkopfh. **103**: (Abst.) 68, 1919.
78. Laryngoscope **29**:447, 1919.
79. Rev. de Laryngol., Otol. et Rhinol., (June 15), 1920.

tions of the palate in nine, perforations of both septum and palate in twelve, syphilitic osteitis in twenty, and syphilis of the larynx in two cases. No case of syphilis of the brain and spinal cord, or syphilis of the labyrinth or syphilitic paralysis of the larynx was seen.

Richardson [80] reports a case of condyloma of the anterior nares, an unusual manifestation of syphilis, that responded promptly to arsphenamin.

Mahler [81] reports a case of hereditary syphilis in a girl, aged 14, who had parenchymatous keratitis. Deafness developed suddenly and is complete in the right ear and severe in the left. Caloric and rotation nystagmus are absent. The fistula symptom was present.

Goeckerman, Barlow and Stockes [82] found shortened bone condition in 78 per cent. of cases of syphilis. The test has only a restricted value.

Peck's [83] experience is that chronic septic foci of the teeth and tonsils cause or contribute to thyroid disease. Operation should be done in all cases of exophthalmic goiter if removal of existing foci has not cured, providing there is not marked cardiac degeneration. A thyroid gland causing interference with respiration, speech, digestion, or a laryngeal cough, should receive early surgical attention. Many large goiters should be operated for cosmetic reasons. A hard nodular goiter in an elderly individual should be operated radically for it is probably malignant. Exophthalmos is apt to persist after thyroid resection and may demand an operation on the orbital walls.

Corwin,[84] in reporting a case of posticus paralysis resulting from a goiter operation, quotes Mayo to the effect that in possibly 10 per cent. of the goiter operations at the Mayo clinic some temporary hoarseness remains afterward, while in 3 per cent. there is permanent difficulty with one cord, or loss of voice. Mathews of the Mayo clinic found the vocal cords paretic in seventeen of 1,000 goiter operations.

80. Ann. Otol., Rhinol. & Laryngol. **28**:786, 1919.
81. Arch. f. Ohren-Nasen- u. Kehlkopfh. **103**: (Abst.) 42, 1919.
82. Am. J. Syphilis **3**:240 (April) 1919.
83. Ann. Otol., Rhinol. & Laryngol. **28**:781, 1919.

American Journal of Diseases of Children

STANDARDS OF BASAL METABOLISM IN NORMAL INFANTS AND CHILDREN *

FRITZ B. TALBOT, M.D.

BOSTON

The advent of less complex methods of determining the basal metabolism of adults has made it possible for a large number of investigators to enter this field of research. The fact that such determinations have been of distinct clinical value in some cases has been shown by the works of DuBois, Means, Boothby and others, and, as a result, many clinicians in hospitals throughout the country are now using the small portable apparatus in their investigations.

Until recently little has been done on the metabolism of infancy and childhood, although occasionally investigators in the adult field have studied the basal metabolism in obscure conditions of childhood. Up to date, however, there has been no normal standard with which to compare these studies, and, as a result, it has been impossible to interpret these findings.

The purpose of this paper is to present in a concise form the basal metabolism curves for infancy and childhood which may be used as standards for comparison by future investigators.

In order to establish the normal basal metabolism of infants and children, a series of investigations by Benedict and Talbot on 258 normal infants and children were carried on over a period of ten years and recently have been reported.[1] These studies have been charted and smoothed curves drawn to show the average trend of the metabolism. A line representing 10 per cent. deviation has been drawn on either side of the average curve to delineate what may be considered a normal variation from the average.

Charts 1 to 6 represent the basal metabolism of normal infants for the first two years of life, and may be used for comparison in studying the metabolism of pathological cases up to two years of age. During this early period of life the changes in the metabolism are so great that the results have been plotted in months rather than in yearly periods.

---

* Submitted for publication, March 29, 1921.

1. Benedict and Talbot: Metabolism and Growth from Birth to Puberty, Carnegie Institution of Washington, Publication No. 302, 1921.
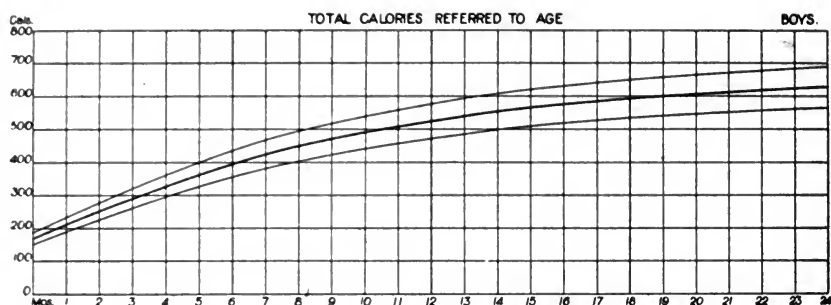
Chart 1.—Basal metabolism of boys during first twenty-four months of age, showing the total calories per twenty-four hours.
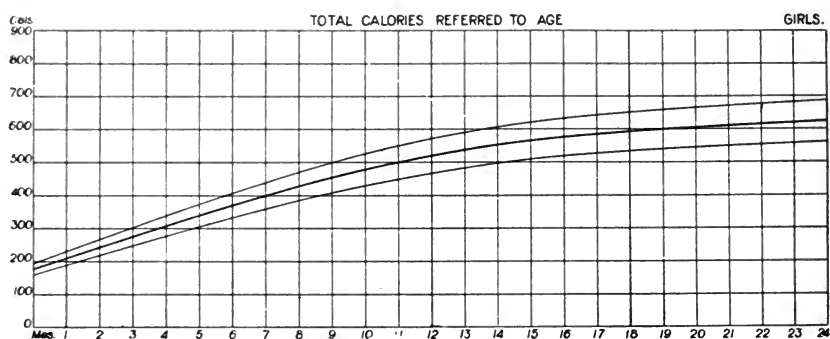
Chart 2.—Basal metabolism of girls during first twenty-four months of age, showing the total calories per twenty-four hours.
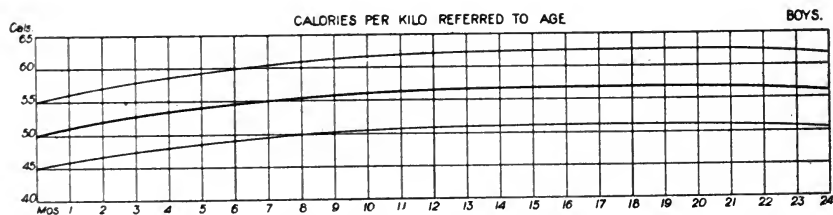
Chart 3.—Basal metabolism of boys, calories per kilogram of body weight per twenty-four hours during the first twenty-four months of age.

The metabolism of the new-born infant, that is during the first few days of life, requires special standards. The average metabolism per twenty-four hours is as follows:

Total = 142 calories; per kilogram of body weight, 42 calories, and per square meter of body surface 612 calories.[2] The metabolism of the new-born infant may be computed very closely by the formula of Benedict and Talbot.[3]

A comparison of the basal metabolism charted in months with that charted in years shows that the curves on the two charts are identical; the former being stretched out to such a degree that the curves are less abrupt and more easily readable.

. Charts 7 to 14 show the curves of the basal metabolism of children from birth to puberty, and include the age periods given in Charts 1 to 6, as well as later childhood. As in the first charts, the area of 10 per cent. deviation is shown by lines on either side of the average curve. The metabolism during puberty will have to be studied further before any standards may be accepted, and the age periods on these charts after 12 years should be taken only as temporary suggestions.[4]

If an investigator wishes to study cases from the point of view of total calories correlated to weight only, the multiple prediction formula [5] may be used. This formula does not make it possible to study the metabolism per unit of weight or per unit of body surface without further computation.

Qualifications necessary for basal metabolism.—To determine the basal metabolism of adults it is necessary for the patient to be in the "postabsorptive state," which occurs about twelve hours after the last meal, to have a normal temperature, and to be in absolute physical repose. In infancy, on the other hand, the determination of the basal metabolism is complicated by the fact that the infant must be fed in order to keep it quiet over the necessary period. The rise in metabolism due to restlessness and crying is so great that it overbalances the increase in metabolism due to the "stimulating action" of food; the

---

2. Benedict and Talbot: The Physiology of the New-Born Infant, Carnegie Institution of Washington, Publication No. 233, 1915.

3. Total calories $= 1 \times 12.65 \times 10.3 \sqrt[3]{wt^2}$. In this formula $1 =$ length, $12.65 =$ constant, $10.3\sqrt[3]{wt^2} =$ Lissauer's formula for body surface.

4. Papers by F. G. Benedict and M. F. Hendry on the Basal Metabolism of Girl Scouts are appearing in the Boston M. & S. J. **184**:217, 282, 297 (March) 1921.

5. Benedict: Proc. Nat. Acad. Sc. **6**:7, 1920, applied the multiple prediction formula which is derived by biometric analysis of the basal metabolism of 136 men by himself and Dr. Harris to the boys in the Benedict and Talbot Series. The formula: $h = 66.4730 + 13.7516w + 5.003s - 6.7550a$. In this formula $h =$ total heat production per 24 hours, $w =$ weight per kilogram, $s =$ stature in centimeters, $a =$ age in years. It was found that the metabolism of boys who weighed above 10 kg. could be predicted with an average deviation from the individual prediction of ± 56 calories or 6.3 per cent.
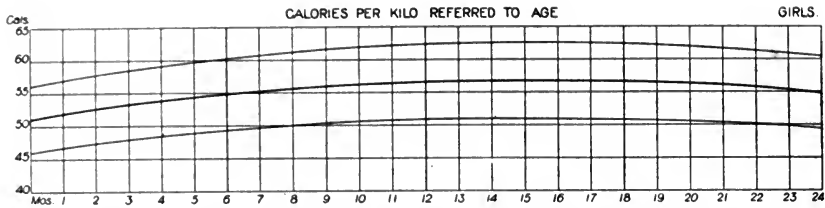
Chart 4.—Basal metabolism of girls, calories per kilogram of body weight per twenty-four hours during the first twenty-four months of age.
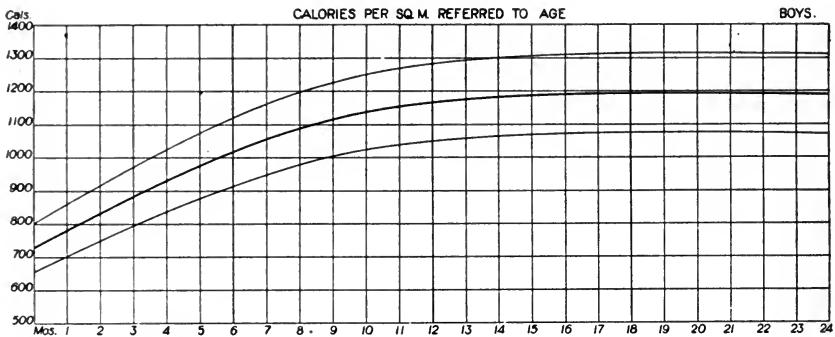
Chart 5.—Basal metabolism, calories per square meter of body surface per twenty-four hours of boys during the first twenty-four months of age.
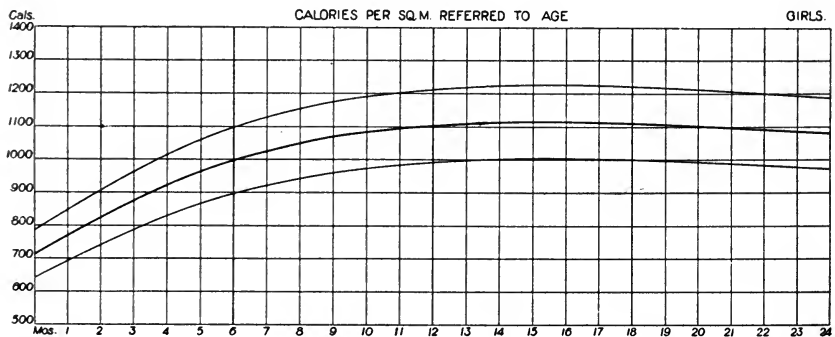
Chart 6.—Basal metabolism, calories per square meter of body surface per twenty-four hours of girls during the first twenty-four months of age.
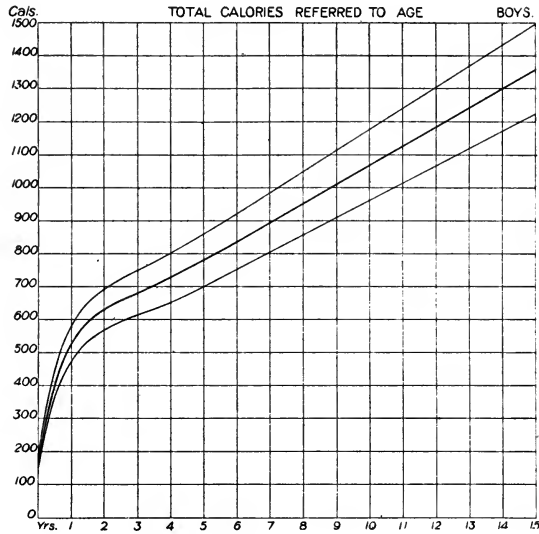
Chart 7.—Basal metabolism, total calories per twenty-four hours of boys by years. The curve is projected from 12 years onward.
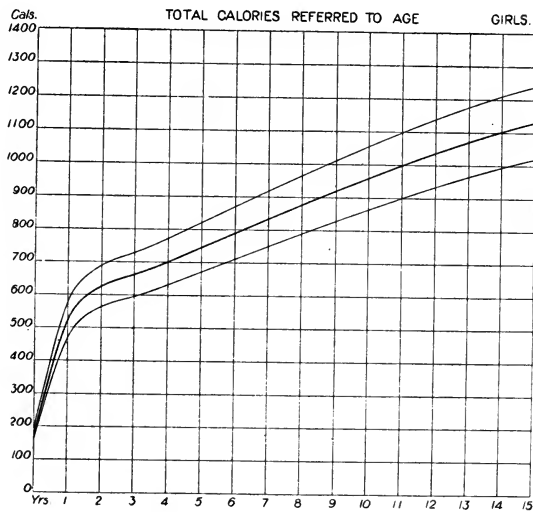
Chart 8.—Basal metabolism, total calories per twenty-four hours of girls by years. The curve is projected from 12 years onward.

increase in basal metabolism due to the "stimulating action" of food being from 9 to 14 per cent., and that due to muscular activity often from 30 to 40 per cent., and occasionally more than 100 per cent. The curve of the "basal metabolism" during this age period is higher than absolute basal figures because of the "stimulating action" of the food. On the other hand, experience has shown that the basal figures obtained after the ingestion of food are usually lower than figures that might be obtained during fasting. The basal metabolism, therefore, during the first two years of life may be more closely approximated with food in the stomach than during starvation, and these curves may be taken, to all intents and purposes, as standards with which to compare the metabolism of infants studied under identical conditions.

To determine the basal metabolism of children over 2 years of age, it is essential that the patient be in absolute physical repose, without food in the stomach, and, if possible, asleep. In older children, however, it is more difficult to obtain sleep.

Determinations of the basal metabolism of infancy and childhood have been made for the most part in a respiratory chamber. The technical difficulties involved by the use of this apparatus, however, make the determinations both difficult and expensive. Investigations made with the portable apparatus, on the other hand, are simpler, but since this apparatus requires the use of a mouthpiece and noseclip, it is unsuited for work with children. The only practical apparatus for determining the basal metabolism of children, therefore, is the respiratory chamber, and it is probable that this is the only method which will be practical for children up to 12 years of age. All so-called basal determinations with an apparatus requiring the use of a mouthpiece and noseclip should be looked on with suspicion until the results have been checked up with those obtained on the same child in a respiratory chamber.

Studies of the basal metabolism have shown that sex influences the height of the basal curve in children. These differences have been chartered and published.[6] The variation due to sex is less marked in infancy than in later childhood, but enough variation is found during this period to warrant the plotting of separate charts for each sex.

Basal metabolism determinations may be made in any well fitted up laboratory suited for this purpose. The great difficulty lies in the correct interpretation of the results. It is necessary to know what are the normal variations of metabolism, and what factors lead to these variations. This would be very simple if all normal children of a given age were of the same weight, height and physical conformity. If this were so, their basal metabolism would, in all probability, fall within 6 per cent. of the average curve. The physical development of grow-

6. Carnegie Institution, Washington, Publication No. 302, pp. 179-181.
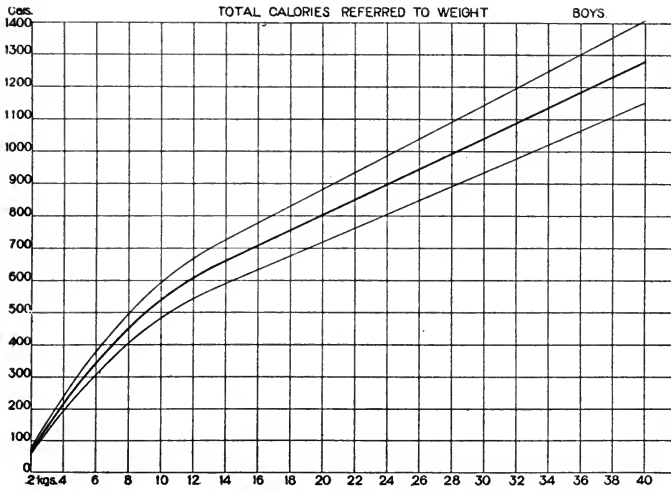
Chart 9.—Basal metabolism of boys, total calories in twenty-four hours at different weights. The curve is projected from 32 kg. upward.
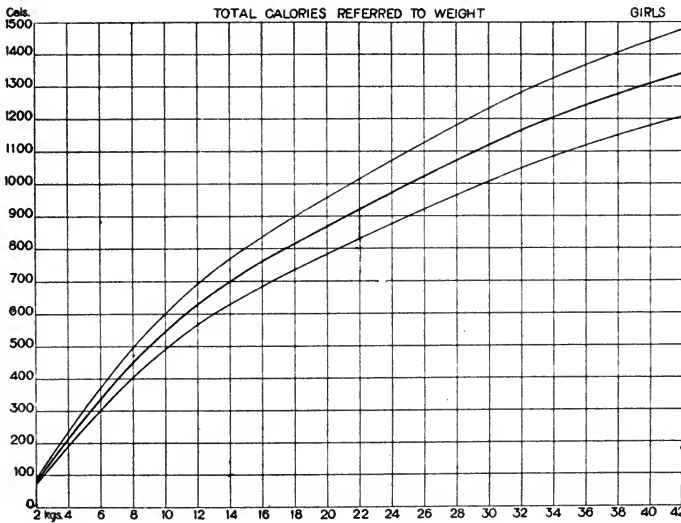
Chart 10.—Basal metabolism of girls, total calories in twenty-four hours at different weights. The curve is projected from 32 kg. upward.
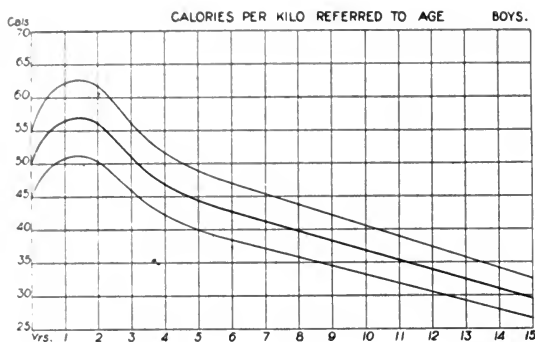
Chart 11.—Basal metabolism, calories per kilogram of body weight for twenty-four hours of boys at different ages. The curve is projected from 12 years upward.
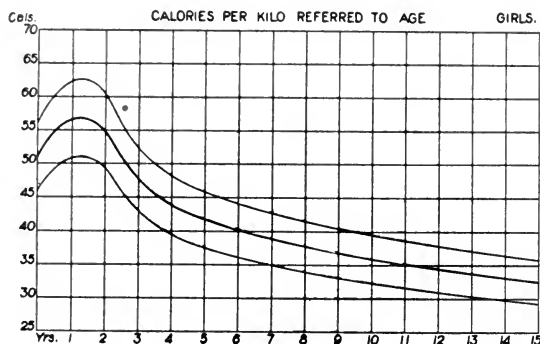
Chart 12.—Basal metabolism, calories per kilogram of body weight for twenty-four hours of girls at different ages. The curve is projected from 12 years upward.
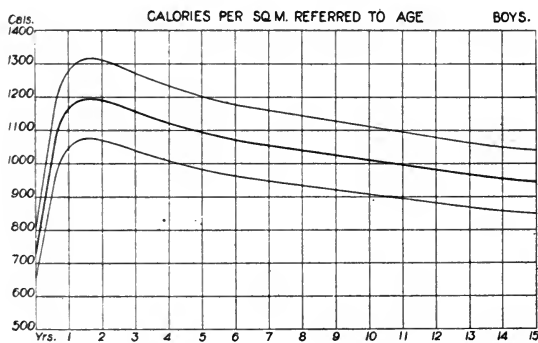
Chart 13.—Basal metabolism, calories per square meter of body surface for twenty-four hours of boys at different ages. The curve is projected from 12 years upward.

ing normal children, however, varies within wide limits, and, consequently, variations occur in their basal metabolism. Variations within 10 per cent. either side of the average curve have been taken arbitrarily as the extreme limits of variation of children with approximately average development. A careful study of the cases outside the 10 per cent. limits has shown that they belong to certain groups.

Children who are above the average height and weight for the age and who have a normal amount of muscle and fat, are found to have a total metabolism of more than 10 per cent. above the average for the age, but within the 10 per cent. variation when applied to the total metabolism for their weight and per unit of body weight and body surface. On the other hand, a child that is of normal development but small for the age, has a total metabolism of more than 10 per cent. below the metabolism for the age but within 10 per cent. of
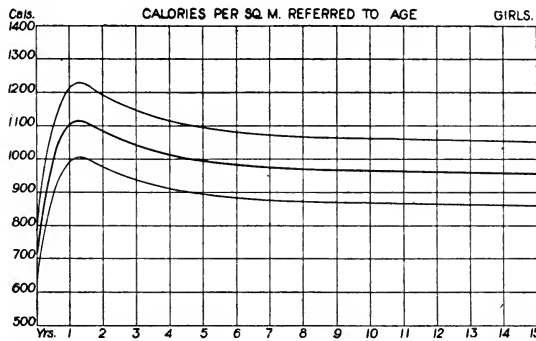
Chart 14.—Basal metabolism, calories per square meter of body surface for twenty-four hours of girls at different ages. The curve is projected from 12 years upward.

the total metabolism for the weight and per unit of body surface and body weight. In both these instances, the total metabolism conforms with the expected metabolism for the weight but not for the age.

Secondly, children who are of average height but over-weight have a total metabolism which usually falls within the average limits for the age and per unit of body surface. Those who are fatter than the average have a metabolism per kilogram of body weight below the 10 per cent. variation, and those who are thinner than the average are more than 10 per cent. above the average; the extent of the variation depending on the relative amount of body fat. This is, in all probability, due to the fact that fat is an inert substance in so far as the energy metabolism is concerned.

Thirdly, in children that are both large and fat, the total metabolism tends to fall within the average limits for the age, but the metabolism per unit of weight and per unit of body surface falls below the 10

per cent. variation; while those children who are small and thin fall above the 10 per cent. variation per unit of weight and per unit of body surface. The metabolism per unit of body surface is less affected in these comparisons than the metabolism per unit of body weight.

These variations in the metabolism are more pronounced in infancy than in later life. Studies of the metabolism of the first two years of life, therefore, are much more difficult to interpret than are those of older children.

These charts are presented as standards of the average basal metabolism of average normal children. The basal metabolism of the majority of cases studied up to date fall within 10 per cent deviation of the average line given in the charts. Physical development of the child plays a part in influencing the metabolism in childhood, but the proportion of body fat plays a still greater part in causing a deviation from the average.

THE REFLEXES IN EARLY INFANCY *

CHARLES W. BURR, M.D.

Professor of Mental Diseases, University of Pennsylvania

PHILADELPHIA

Gottfried Engstler [1] found that in 232 children in the first week of life, and with sound nervous systems, the plantar reflex consisted of dorsal flexion of the toes, whereas in two children there was plantar flexion and in eight no response was elicited on stroking the sole. Between the second and eighth week, ninety-nine showed dorsal flexion, one child showed plantar flexion, and eight gave no response. In the third half year, sixty presented dorsal flexion, thirty gave no response, and forty had plantar flexion. On the other hand, in the third year, five presented dorsal flexion, five gave no response, and ninety-five had plantar flexion.

M. A. Léri [2] in 166 infants found extension of the toes on stroking the sole the rule at birth and flexion the exception, whereas after three years, flexion was the rule and extension the exception.

John Lovett Morse [3] concluded after the examination of 254 infants during the first twenty-three months of life that

It is evident that there is no constant plantar reflex in the first year, and that while the reflex approaches the adult reflex during the second year, it is still inconstant. It is also evident that since there is no constant reflex under normal conditions during the first two years, no conclusion can be drawn from the presence, absence, or character of the reflex in the diagnosis of abnormal conditions of the nervous system at this age.

Kalischer [4] as quoted by Morse,[3] states that no conclusions can be drawn concerning the plantar reflex in babies because of the many voluntary motions. If, however, a certain movement constantly follows every irritation and is confined to one side it is significant of disease.

J. P. Crozer Griffith [5] states:

Some of the reflex movements which persist throughout life, as the plantar and the patellar reflexes, are, on the whole, not so uniformly well shown in the first and second years as later. Others, such as the abdominal, cremasteric, corneal and pupillary reflexes, are fully developed from birth.

1. Engstler, G.: Wien. klin. Wchnschr. **18**:567 (June 1) 1905.
2. Léri, M. A.: Gaz. d. mal. infant. **5**:277, 1903.
3. Morse, J. L.: Pediatrics **11**:13 (Jan. 1) 1901.
4. Kalischer: Virchows Arch. f. path. Anat. **155**:486, 1899.
5. Griffith, J. P. C.: The Diseases of Infants and Children, Philadelphia and London, W. B. Saunders Co. **1**:65, 1919.

G. L. Walton and W. E. Paul [6] "question the existence of a characteristic toe reflex at this period" (early Infancy). They note that several times when a baby was examined a second time after a very short interval, the examiner not knowing the little trick being played, the two descriptions of the reflex movements were contradictory.

There are practical difficulties in testing the reflexes in babies not present in older people. The new-born and very young are in a state of almost constant movement, except during sleep, on account of the numberless stimuli from within and without, stimuli to which older children pay no attention. Further, if the leg is held by the examiner while trying to get, say, the plantar jerk, the infant often immediately and persistently resists (holds the leg in rigid flexion or extension) and hence the reflex does not appear. The patellar tendon is very small in babies, and to percuss it is not always easy. In a crying baby often no reflex movement can be obtained on account of the general muscular rigidity, while in the same baby at rest all reflexes may be prompt.

Curiously enough, muscular contraction in other parts of the body (the leg remaining relaxed) did not (in the children I examined) reinforce the knee jerk; e. g., if a child grasped something vigorously in its hand while the knee jerk was being taken, the response was neither quicker nor more rapid, nor did the foot go through a larger arc than when the child was at absolute rest.

I have examined at the Children's Hospital and the Philadelphia General Hospital (Blockley) sixty-nine infants. The ages varied as follows: 1 hour or under, 3; between 1 hour and 24 hours, 11; more than from one day to 7 days, 28; from 8 to 30 days, 15; from 31 to 90 days, 12.

Twenty-seven infants were of negro blood of varying degree and a study of them revealed no racial peculiarity in the reflexes. The children were all free from any disease of the nervous system, save one child (9 days old) who had a congenital peripheral facial palsy.

As to diseases other than a nervous affection, two had been operated on for pyloric stenosis; one had infantile atrophy; one was a premature birth (7 months). In the seven months baby, when the child was 46 days old, the knee jerk was normal; the abdominal jerk was present only on stimulating the lowest third of the belly of the muscle ; the chin jerk was present, and while on the right the plantar jerk consisted in extension of the toes, on the left, during repeated trials, there was no toe movement but only withdrawal of the whole foot. Barring this dif-

---

6. Walton, G. L., and Paul, W. E.: Nerv. & Ment. Dis. **27**:305 (June) 1900.

ference in the plantar jerk on the two sides, there was no greater
variability in the reflexes than is found in healthy infants.

As to the health of the mothers, two had had puerperal eclampsia.
The child of one (1 hour old) gave slow, deliberate extension of all
toes, a very prompt Achilles jerk, prompt knee jerk on both sides with
contralateral adduction of the thigh, and absent scrotal jerk. The
child of the other, when 6 days old, gave slow extension of the great
toes with no movement of the other toes and normal knee jerks, and
percussion of the chin caused twitching of the upper lip. There was
one imbecile mother. Her child (26 hours) had normal knee and
Achilles jerks and extension of all toes.

The knee jerk was examined in sixty-six children and was present
in sixty-one. The ages of the five in whom it was absent were: one
less than 1 day; one, 2 days; two, 3 days; one 4 days. It was present
in three children less than one hour old. Out of ten more than one
hour and less than one day old it was present in nine and absent in
one. In those more than one day and less than 8 days old, it was present
in twenty-one and absent in four. It was present in all children more
than 8 days old. In one white boy, 6 days old, however, who showed no
signs of disease of any kind, the right knee jerk was prompt and
easily gotten; the left was absent. He also had no true plantar jerk but
only withdrawal of the foot; no cremasteric jerk and no Achilles
jerk. His case is proof of the fact that differences in the knee jerk
on the two sides in a child is not indicative of disease. In one girl
in whom the knee jerk was absent at 19 hours, it was present ten days
later, and in a boy in whom it was absent at 3 days it was present four
days later.

Even in the adult the Achilles jerk is absent sometimes, and its
presence or absence can only be determined after careful examination
in a proper posture. I examined fifty-two of the infants and found it
absent in thirty. In two examined within one hour after birth it was
present in one, absent in one. Whereas, in many of the children the
knee jerk was as good as in the adult, in most of the children the
Achilles jerk was only obtained after many attempts and then it usually
was very feeble; occasionally, it was as good as one ever sees in
adults.

There are many difficulties in studying the plantar jerk in infants
on account of their restlessness. I regarded as a plantar reflex only
flexion or extension of the toes. In nine instances, though the toes
moved, the movement was so erratic that I could form no judgment.
In nineteen others there was no movement of the toes of any kind, no
matter what part of the sole was stimulated, and, incidentally, I found

that stroking the outer edge of the sole, in general, gave the best response. In twenty-five cases there was definite extension of the toes, and in sixteen there was flexion. Within an hour of birth the plantar jerk may be well established. Thus, one boy, one hour old, showed beautiful and deliberate extension of all the toes with fanning. His knee and Achilles jerks were also well developed. Another boy of the same age showed a constant slow flexion and a third had no plantar response of any kind. In one boy, 2 days old, and in another 3 days old, there was a quick extension of the toes followed by slow flexion and bunching of them together as if trying to grasp an object with all the toes at once. The grasping movement was just that which our far off arboreal ancestors must have made as they swung from bough to bough and caught at support with the feet. In another boy, 4 days old there was first extension and then flexion of the great toe without any movement in the other toes.

I did not examine the chin jerk in a large enough number (twenty-five) for my results to have any statistical value. Suffice to say, it may be but is not always present within one day of birth. In one girl, 31 days old, the reflex consisted in a closing of the lips, in another girl, 8 days old, and a boy, 6 days old, there was only a twitching of the upper lip.

I examined the abdominal jerk in twenty infants and found it absent in seven. It was present in two under 4 days old; on the other hand, it was absent in four out of seven between 2 and 3 months old. In four it was obtained only on stroking the skin over the lowest third of the rectus abdominis muscle.

CONCLUSIONS

1. The deep and superficial reflexes (i. e., knee, Achilles, chin, plantar, abdominal) may be present at birth but the absence of one or all in early infancy does not indicate disease.

2. The plantar jerk is very variable. It may be absent up to the third month or longer, or there may be extension or flexion of the toes, or at one time there may be one movement, at another the other. Most frequently there is extension. The movement may be rapid or deliberate.

3. The Achilles jerk is very frequently absent at birth. (How late in life it may appear is unknown).

4. Sometimes the abdominal jerk can be obtained only on stimulating the lowest third of the muscle.

5. Whether the occasional absence of the knee jerk in healthy adults (1 in 500) is congenital or the result of disease in early life cannot

be decided in the absence of a complete medical history. (Diphtheria may permanently abolish it without persistence of other signs of nervous involvment).

6. When the reflexes appear after birth, their appearance does not occur in any regular order.

THE FACTOR OF THE POSITION OF THE DIAPHRAGM IN ROENTGEN-RAY DIAG-NOSIS OF ENLARGED THYMUS *

H. J. GERSTENBERGER
CLEVELAND

The diagnosis of the presence of an enlarged thymus by percussion, I believe, has been considered by most physicians to be a difficult and uncertain performance.. Therefore, the advent of roentgen ray was hailed and is generally still believed to be a safe and dependable diagnostic method as applied to the thymus.

An experience during the past winter has convinced me that the diagnosis of an enlarged thymus with the aid of the roentgen ray is also liable frequently to be very uncertain and to be a source of erroneous interpretations and findings.

A brief recapitulation of this experience will bring out the interesting points.

REPORT OF CASE

In July, 1919, in the absence of the family physician in the army, I was called to atttend the child of a colleague, whose skin was scaly and itchy and who was breathing with difficulty. The boy, 12 months old, was quite well developed and nourished, showed a mild rickets, a distinct but slight eczema of the face, chest and arms, causing a great deal of itching, and a decided emphysema, accompanied by wheezing and a somewhat labored expiration. The spleen was not palpable and the posterior cervical lymph nodes were somewhat increased in size and in number, as is usually the case in exudative children.

The child had since his third week received a Walker-Gordon mixture, and recently has been given straight cow's milk and vegetables.

The condition was considered to be due either to a hypersensitiveness to some food constituent or to an exudative diathesis.

A skimmed milk diet, atropin sulphate in increasing drop doses, to physiologic limit, and 10 per cent. tricalcium phosphate in cod liver oil were ordered, and were followed by a decided improvement.

During August, 1919, the family physician returned, found an increased thymic dulness, and requested a roentgenogram, which showed a wide shadow, especially to the right but also to the left of the sternum, and which the roentgenologist stated was caused by an enlarged thymus (Fig. 1). Consequently the family physician stopped the atropin and had the thymus exposed every three to four weeks for a total of five exposures.

The condition of the child, however, grew slightly worse instead of better, and the thymic shadow remained the same, so that the roentgenologist advised against further exposures. The family physician then reordered the atropin in the form of belladonna in small doses. The child improved again and breathed in a nearly normal manner during the latter half of November, 1919.

During the first days of December he contracted a cold and in the night of December 3 he became severely asthmatic and somewhat cyanotic. I saw him with the family physician December 4 and he was then taken to Lakeside Hospital for diagnosis and treatment.

Nov. 10, 1919, the family physician had his assistant make cutaneous scratch tests with different proteins in simple saline solution, which were all negative. The proteins used were as follows: wheat, cow's milk, rice, potatoes, egg white, beef, oats, tomato, horse hair, pneumococci, staphylococci and ragweed.

December 4 at the hospital the diet and therapy of July, 1919, were reordered and the child improved.

December 5 a roentgenogram was taken, which showed a much smaller shadow than had ever been seen in this case before and really one that was practically normal (Fig. 2). This finding convinced the family physician that after all the improvement noticed in the latter half of November, 1919, was due to a reduction in the size of the thymus, which had occurred since the last picture had been taken in October.
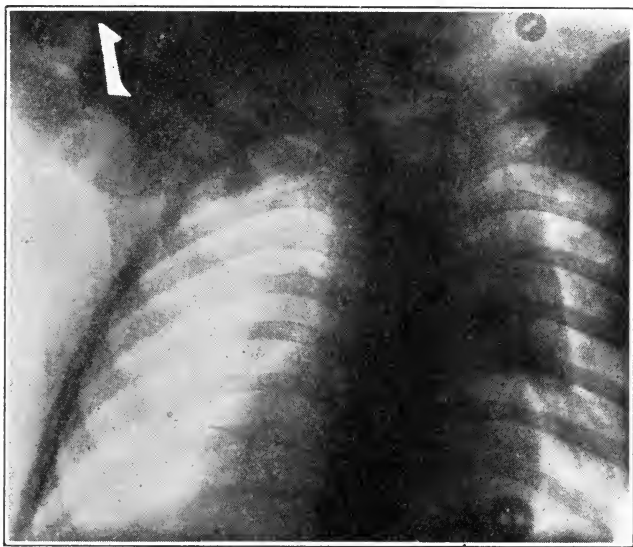
Fig. 1.—Roentgenogram made Aug. 5, 1919, showing decided shadow in thymic region, especially on right side. Note sharp, angular projection at right lower end of shadow.

Intracutaneous sensitization tests were carried out at the hospital from December 8 to 13 and showed the child to be negative to cow's milk casein, cow's milk albumin, strawberry, orange and tomato, questionably positive to cow's milk allergen and enormously sensitive to egg yolk allergen and egg yolk albumin. The latter two tests were accompanied by a severe anaphylactic shock that was relieved by the administration of adrenalin subcutaneously.

December 16 two roentgenograms were taken, both of which showed an abnormally large shadow in the thymic region, in other words, just the opposite from the last findings in the plates of December 5.

The improvement of the child, that was still getting atropin in increasing doses, cod liver oil with tri-calcium phosphate and skimmed milk, continued, and did not correspond with the decided reversal in the shadow in the roentgenogram.

A fluoroscopic examination was immediately made and succeeded in establishing the interesting fact that the two extremes of normal narrow shadow, on the one hand, and a markedly wide and seemingly abnormal thymic shadow on the other, corresponded in the former with the end of a deep inspiration and in the latter with the end of a deep and forceful expiration.

The development of the shadow in its most marked form under the fluoroscope may well be compared with the filling of miniature lungs which paradoxically decrease in size with inspiration and collapse entirely with a deep taking in of air. In order, however, to get this markedly increased shadow which in this patient was always greater on the right than on the left and frequently present only on the right side, especially if the expiration had not been of the extreme type, it was necessary to have the child cry vigorously and establish a prolonged and forceful expiration.

It is especially significant to note that the expiration had to be forceful, for at times I saw a prolonged expiration produce an increase in the shadow of the thymic area without presenting the beautifully clear picture to either side of the vertebral column, simulating as stated above the filling to capacity of a miniature pair of lungs with distinct outlines, definite and sharp borders. Whenever I have seen this picture produced under the fluoroscope it has seemed to me that the diaphragm moved distinctly upward and was directly or indirectly

Fig. 2.—Roentgenogram made Dec. 5, 1919, after repeated exposures (from four to five). Shadow in thymic region decidedly less and practically normal.

responsible for it. Likewise, I have always seen a distinct descent of the diaphragm, accompanied by a very deep and very voluminous taking in of air, precede the rapid and complete disappearance of the abnormal shadow.

Unless this deep inspiration and distinct drop in the position of the diaphragm occurred, the shadow would only get smaller and indistinct as it partially receded toward the middle line.

Whenever a clear and marked shadow was seen under the fluoroscope one could note the outlines of the lobelike shadow on either side, but again always more distinctly on the right than on the left, and a definite and sharp but slightly rounded angle at the extreme outer and lower pole, separated by a clear rather straight space from the heart and distinctly away from it and pointing out into the area of the lungs.

At no time was any pulsation noticed in any of the shadows or in any part of a shadow, when seen under the fluoroscope in this patient.

It is further significant that only when a forceful expiration was established could a lobelike shadow be seen to the left of the middle line and then never as clearly as on the right side. When the shadow on the right side was medium in degree no definitely outlined form could be seen on the left side. All of these pictures were seen much better in the fluoroscope than in the roentgenogram. However, on three of the pictures a less intensive, lobelike somewhat hazy shadow can be seen to the left of the middle line, which together with the shadow on the right side sits over the heart in the form of a blunted cone with a distinct lower border *separated at the side,* especially on the right side of the heart, *by a clear sharp space as described above, and forming a distinct angle, pointing outward and away from the heart.*

The child went home for the Christmas holidays and returned to the hospital January 7, where it remained for ten days. During this time four attempts were made to register on plates in prompt and, if possible, in immediate succession pictures of the two extremes seen with the fluoroscope, so as to be able to present to those interested in the roentgen-ray diagnosis and therapy of the thymic gland, the customary before treatment and after treatment pictures only obtained, however, in this child both on the same day and at the same sitting.
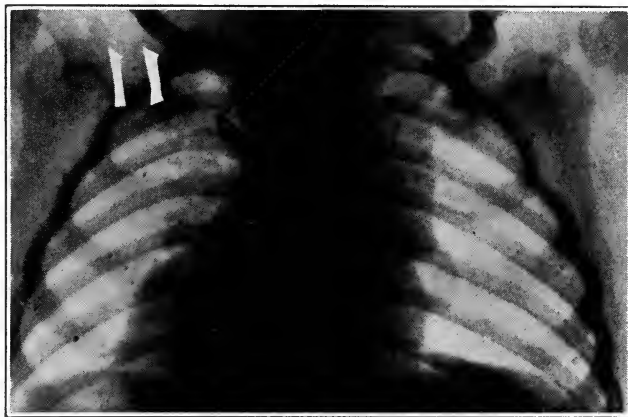
Fig. 3.—Roentgenogram made Jan. 17, 1920, showing return of decided shadow in thymic region, especially on right side, and practically identical with shadow shown in Figure 1. Note again the presence of the same sharp, angular projection at the right lower end of shadow.

January 8 both plates showed wide shadows to the left as well as to the right, but much more distinctly on the latter side.

January 12 it was again impossible to obtain photographs during the height of inspiration and both plates showed in consequence decided shadows to the right.

The pictures taken January 15 were out of focus and could not be utilized.

Finally January 17 we were able to get first a markedly wide shadow involving both sides (Fig. 3) and immediately afterward a narrow shadow that was practically normal (Fig. 4) and just like the two obtained December 5. In other words, we did obtain in the same child at the same sitting both a normal and an abnormal shadow in the thymic region, certainly a difficult finding to interpret.

COMMENT

Numerous questions difficult to answer immediately arise. Is this shadow due to the thymic gland or to something else as the superior vena cava or the right auricle? Is the thymus really abnormally large or is its size actually within the variable normal limits, and is it brought into the plate in the form of an abnormal shadow simply as a result of the operation of some abnormal factor such as an abnormally increased intrathoracic pressure especially in this child, whose lungs, owing to a possibly at times still existing construction of the bronchioles, might retain more air than those of a normal child at a given stage of respiration and so might enable the production of an intrathoracic pressure in forced expiration that would be greater than that found in a normal child?
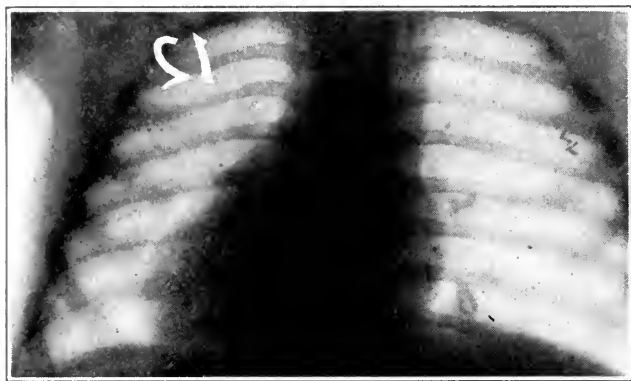
Fig. 4.—Roentgenogram made Jan. 17, 1920, five minutes after obtaining Figure 3, and showing just the opposite finding, namely, a practically normal shadow in the thymic region, and corresponding to Figure 2 obtained Dec. 5, 1919.

Or are the intrathoracic factors causing the thymus to stand out in this so-called abnormal manner really normal and simply abnormally utilized in the sense of hypereffectiveness?

For instance, is it possible that one normal child can push his diaphragm up more effectively or increase his intrathoracic pressure more decidedly than another normal child of the same age and weight? Again, if it is the thymus are its lobes mechanically pushed upward and outward by the ascent of the diaphragm or are they enlarged by a sudden filling with blood as a result of the establishment of an abnormal disproportion between the outflow and the inflow of blood into the gland? Or is its coming out into view due only slightly to the possible effect of the vascular supply on the thymus and mainly due to a following of a mechanical path of least resistance, as a result of a markedly increased intrathoracic pressure produced by various factors, but

recorded best by the ascent of the diaphragm? Does the varying topographical relation of the lungs to the thymus play a part?

Why is the shadow more often present on the right side, and when also present on the left, less distinct than on the right? Is this shadow on the right side really due to the thymus or is it produced by the superior vena cava and right auricle? If it is produced by the thymus is it caused by its close proximity to the just mentioned venous structures? Or is it due to possibly more rapid enlargement of the right lobe than of the left lobe of the thymus, or is it mechanically advantageous under an increased intrathoracic pressure for the right lobe to move out before the left?

Is such a freedom of mechanical mobility of the lobes within the sac of the thymus possible, or is it necessary that a force from within such as would be represented by the filling of the thymus with blood be developed to force the lobe outward in the manner observed?

These questions are all of importance, and I do not see how we can answer them with positiveness until further data are at hand. Definite contradictions exist in the literature regarding most of these points. I have been unable to find satisfactory data regarding the blood supply of the thymus, especially regarding the proportion existing between the inflow and outflow.

Rehn,[1] Hotz[2] and Hart all think that the exit venous channels are Gesellsch. f. Chir., April, 1906, 35th Congress, p. 364.
relatively better developed than arterial inflow vessels, and yet Klose,[3] notwithstanding the fact that he quotes Hotz and Hart as his authorities, expresses just the opposite view, based mainly on the findings of Siegel,[4] who reported in one case the presence of a net work of fine veins on the circumference of the gland and the absence of larger venous channels. Siegel, however, does not attach the same generalization and significance to this individual observation.

Rehn, in 1906, observed at operations on the thymus a regular downward movement of the thymus with inspiration and an ascent with expiration. He makes the further comment that the more forceful the inspiration or expiration the greater the descent of the thymus in the one instance and the ascent in the other, and with deep inspiration the thymic gland is aspirated as it were into the thorax, whereas by severe expiration as during crying, coughing, the gland is forced up out of the chest.

Rehn claims that this physiologic up and down movement of the thymus is responsible, when it is enlarged, for the difficulty in breathing

1. Rehn, L.: Die Thymusstenose under der Thymustod, Verhandl. d. Deutsch.
2. Hotz, G.: Die Ursachen des Thymustodes, Beitr. z. klin. Chir. **55**:515, 1907.
3. Klose, H.: Beiträge zur Pathologie und Klinik der Thymusdrüse, Jahrb. f. Kinderh. **78**:653, 1913.
4. Siegel: Berl. klin. Wchnschr., No. 40, 1896.

that is noticed in some cases at beginning of inspiration, by fitting better and more snugly in the upper opening of the chest at the end of expiration and so acting as a more tightly fitting valve.

Benjamin and Goett,[5] in presenting their experiences at Pfaundler's clinic with roentgen-ray studies of the thymic gland in infants, report an exactly similar observation as the one made by me in this patient, with this difference, however, that the shadow, as observed under the fluoroscope, increased with the descent of the diaphragm and decreased with the ascent. They come to the provisional conclusion that the abnormal picture was produced by the distention of the vena cava and not by the thymus. Later on in their article, however, they modify this conclusion by stating that, according to their recollection, the child cried at the time when the picture of the abnormal shadow was obtained, and was quiet when the good shadow was procured.

If their provisional conclusion is the right one, then the interpretation given by them would seem to be correct from a physiologic point of view. But, as they remark, there is no uniformity of opinion in the literature as to whether the heart in adults during inspiration is wider or smaller than it is during expiration, or vice versa.

Grödel [6] and Dietlen [7] are of the opinion that the descent of the diaphragm produces an inspiratory narrowing of the cardiac shadow, and that the ascent produces an expiratory widening, while Holzknecht and Hafbauer (quoted by Benjamin and Goett) find a widening of the shadow during the entire inspiration.

Dietlen bridges the two contradictory views by admitting a widening of the cardiac shadow in early inspiration due to the sudden filling of the superior vena cava and right auricle as the result of the suction effect during the early part of inspiration.

Benjamin and Goett also quote d'Oelsnitz and Paschetta [8] as having called attention to the part played in infants by the large vessels in the widening of the shadow at the base of the heart and to the fact that this widening is influenced by respiration in the sense that the shadow becomes wider in expiration and narrower in inspiration.

In addition these authors further claim that an enlarged thymus appears mainly to the left of the vertebral column. So one can readily agree with Benjamin and Goett that a subject that at first glance seems

5. Benjamin, E., and Goett, T.: Zur Deutung des Thoraxradiogramms beim Säugling, Deutsch. Arch. f. klin. Med. **107**:509, 1912.

6. Grödel, F. M.: Röntgenkinematographische Studien über Herzgrösse und Herzlage, Ztschr. f. klin. Med. **72**:310, 1911.

7. Dietlen, H.: Ergebnisse des medizinischen Röntgenverfahrens für die Physiologie, Ergebn. d. Physiol. **10**: 1910.

8. d'Oelsnitz and Paschetta: Bull. de la Soc. de Pediat, Paris, 457, 1911. Quoted by Benjamin and Goett: Deutsch. Arch. f. klin. Med. **107**:514, 516, 1912.

simple and clear, when viewed from the standpoint of opinions as written down in the literature, is complicated and difficult.

Benjamin and Goett were checking Hochsinger's [9] claim that the stridor congenitus was caused by the presence of an enlarged thymus, and that this enlarged thymus could be found in the roentgenogram. They had occasion to perform a necropsy on a 7-month-old infant killed in an accident and who also had a congenital stridor and of whose thymic area a roentgenogram had been made. A 20 gm. thymus was found and neither was it nor any other gland in the place where a shadow had been obtained in the plate. This fact, of course, does not prove that the thymus was not concerned in producing the shadow during life.

Again in another infant, the child of a wet nurse, who had never had a congenital stridor but who had frequently showed in the roentgenogram the presence of Hochsinger's shadow and on whom a necropsy was made after an acute illness of six days' duration they found only a very small thymus weighing hardly 3 gm., and concluded that it could not have been a factor in the production of the shadow in this child.

It is well to remember in this connection that Benjamin and Goett found their shadow, as observed under the fluoroscope, during inspiration and not during expiration, and therefore they could hardly expect the thymus to be a factor unless it be of enormous size.

Benjamin and Lange [10] state "that the breadth of the upper mediastinal shadow varies normally with the age and general condition of the patient, and since it may vary from time to time in the same patient the roentgen-ray diagnosis is not always easy or free from error." They continue further, "in one case not included in this series an apparently normal shadow was obtained when the child was quiet or sleeping, but during a restless crying spell the thymic shadow became greatly enlarged."

"The roentgen-ray shadows of congenital heart enlargements are often confused with thymic enlargements. In all cases in which the roentgen-ray diagnosis seemed doubtful, a roentgen-ray exposure was given as a therapeutic test and this test has proven very reliable."

In other words, Benjamin and Lange have made an observation similar to mine by getting a wide shadow in a crying child—picture in all probability taken in decided expiration—and a normal shadow while the child was quiet and sleeping—picture probably taken in inspiration or in very superficial expiration.

9. Hochsinger: Stridor thymic infant, Wien. med. Wchnschr., No. 45, 1903; No. 33, 1910.

10. Benjamin, J. E., and Lange, S.: Report of Nineteen Cases of Hyperphasia of the Thymus Gland, Treated by the Roentgen Rays, Arch. Pediat. **35**:71, 1918.

These authors do not, however, indicate how they decided in this case, by therapeutic tests or otherwise, whether the infant had an abnormal thymus or not as this child was not a part of the series which they were reporting. Nor do they go into the possible rôle that respiration or the diaphragm might play in the production of this shadow picture.

It would seem as if the therapeutic roentgen-ray tests based on finding a normal shadow would be valueless unless checked by observations made at two different respiratory phases and especially with the aid of the fluoroscope.

The patient forming the basis of this contribution is an excellent example of the case in point. Here we have a boy who has a history of difficult breathing, especially during expiration, accompanied by slight cyanosis, symptoms which very well fit into the picture of a case of so-called thymic asthma, just as they also may be just as well a part of the clinical picture of a child sensitive to proteins, or of an exudative child with asthma. Although he has received sufficient exposures to the roentgen ray, this boy can show, just as you wish, either a normal or an abnormal shadow of the thymic region, corresponding with marked inspiration in the former, and with deep and forced expiration in the latter, but not running parallel to his general condition.

This patient has a definitely abnormal shadow that, in all probability, is produced by forcing the thymus upward and outward, and yet it is also most probable that this thymus is not mechanically concerned in giving him his respiratory difficulty. And in the face of a marked protein hypersensitiveness, accompanied by a mild eczema and expiratory asthma, it is impossible to claim that this boy is one of the thymic cases that are refractory to roentgen-ray therapy and that for this reason his thymus gland has not decreased in size. In other words, unless we find in this boy what, at the present time is considered to be a normal shadow, both in expiration as well as in inspiration, under the fluoroscope, as well as in the roentgen-ray plate, we will not be able to give credit for his improvement to the effect of the roentgen ray on the thymus gland.

Of course seemingly definite cases of clinical thymic asthma in the newly-born have been rapidly and definitely relieved of their symptoms by exposure to the roentgen ray. Usually their improvement has been accompanied by decided narrowing of the shadows, so that the conclusion has been drawn that the betterment was due to the reduction in size of the thymic gland. But in the light of the present case under discussion we cannot be sure that the roentgen ray actually reduced the size of the gland and still it really may have accomplished just that. Further observation on the basis of the experience attained with this patient will help to settle that question. It may be that as a result of the exposure to the roentgen ray the child's condition was improved,

and as a result he was more quiet when later pictures were taken, so that normal shadow may have been produced because the child was more comfortable and did not cry and squirm when the pictures were being taken, rather than because the thymic gland had been decreased in size. It is conceivable that the roentgen ray might influence an internal secretion of the thymus and as a result remove the agent that is responsible for the asthma without at the same time causing any change in the actual size of the gland.

It is necessary to call attention to one of the arguments used by Benjamin and Goett in favor of their opinion that the abnormally wide shadow found in normal children varies according to their condition; the well nourished showing a wide shadow, the poorly nourished a normal shadow. They attributed the variations to the difference in blood volume between the two types of children. While this difference does exist, it is equally true that the size of the thymus gland seems to follow the same rule, being small in the skinny child and large in the well nourished, so that this argument can be applied to one theory with no greater justification than it can to the other. However, one can see how in the well nourished child both factors could operate together to the advantage of a wide shadow, whether it be thymic or nonthymic.

SUMMARY

1. The case of a patient, 17 months old, is presented who under the fluoroscope and in the roentgenogram shows a wide shadow in the thymic region which, according to present conception, is considered abnormal.

2. This shadow in its most marked form extends both to the right and to the left of the vertebral column, while in its mediumly severe form it projects out only to the right.

3. This wide shadow is sharp in outline and has a definite shape, similar to that of a miniature lung, *with an angle at the lower, outer, right side which seemingly cannot be produced by the vena cava, nor by the auricle, as it extends clearly separated from the heart out into the lung area,* and not toward the middle line, as would be the case if a distended auricle were responsible for it. No pulsations were ever seen in the shadow or any part of it, and until contradictory evidence is advanced the shadow is accepted as of thymic origin.

4. *The abnormal shadow can be replaced by one of normal size if the patient takes a deep inspiration.*

5. *The abnormal shadow can be brought out in its most marked form by having the patient expire deeply and forcefully. Both observations can clearly be seen with the aid of a fluoroscope.*

6. The diaphragm, as observed under the fluoroscope, rises with the development of the abnormal shadow and descends with the development of the normal.

7. Frequent exposures to the roentgen ray for a period of over five months have not changed the size of the thymus, nor have they influenced in a dependable manner the general condition of the patient. As a matter of fact, the patient has improved, while his thymic shadow has remained the same. The general improvement can well be explained by the dietetic changes instituted and the administration of atropin.

8. In producing the abnormal shadow in expiration the diaphragm seems to be the most important individual factor, either directly and mechanically by pushing the heart upward and so forcing the thymus in the same direction and also outward when ascending markedly, or indirectly by increasing the intrathoracic pressure to a sufficient degree to move the thymus upward in a mechanical manner, or by retarding decidedly and in forced extreme expiration nearly entirely the venous outflow from the thymus, while still permitting its arterial inflow, and by so creating an acute engorgement and enlargement of the gland, which would cause the above factors to operate even more advantageously, and which would explain better than anything else the miniature lung-like development of the shadow under the fluoroscope.

9. In establishing the return to a normal picture the descent of the diaphragm would seem to operate by relieving the causative factors indicated above, and so allowing the thymus to descend down toward and over the middle of the heart and to empty itself rapidly following the suction effect of inspiration, especially when deep.

10. The wide shadows in their most marked form appeared on both sides, especially when viewed under the fluoroscope, but more on the right than on the left. In mediumly wide shadows only the right side was represented. Consequently, it is not justifiable to conclude that a picture showing a shadow limited to the right side comes from a patient who is unable to develop a shadow on the left side as well, if given the proper conditions, nor can we conclude on the same basis that this shadow on the right side has nothing to do with the thymus gland and has been produced by some other factor such as an enlargement of the vena cava or auricle.

CONCLUSIONS

1. In order to have accurate knowledge as to the actual size of the thymus it is necessary to examine the gland under the fluoroscope and watch its position and condition at the various phases of respiration, especially in the development and at the end of a somewhat

prolonged and forceful expiration, and again during a deep inspiration following the type of expiration just described.

2. If roentgenograms are made, an attempt should be made to get pictures both in deep inspiration and deep expiration. It may be well likewise to first attempt to get a picture while the child is breathing quietly and normally. It must, however, be realized that to procure roentgenograms of the thymus in the different respiratory phases is most difficult, uncertain and time consuming, and, therefore, it is suggested that the fluoroscope be always used to check the findings of the roentgenogram.

3. That unless the thymic shadow is observed as suggested above, a normal shadow obtained following a previous abnormal one does not mean an actual reduction in size of the gland.

4. The findings reported might explain the contradiction of reports according to which clinical improvement was obtained by exposure to the roentgen ray in cases where the thymic shadow was normal. It is possible that these cases really had an enlarged thymus, and that the picture just happened to have been taken during deep inspiration or very superficial expiration. It is, of course, also possible that in such cases the enlargement of the thymus is in the anteroposterior direction.

5. In all probability the position of the diaphragm directly and mechanically, or indirectly by influencing the intrathoracic pressure is more responsible than any other one factor for the difference observed in the pictures taken on the one hand in extreme inspiration and on the other at the end of a marked and forceful expiration.[11]

6. So called improvement in thymic shadow, as presented in Figures 2 and 4, was demonstrated by the fluoroscope to be due not to a reduction in the size of the thymus, but to a change of local conditions in this region, causing, at the end of forced expiration a wide, seemingly abnormal shadow, and at the end of deep inspiration, a narrow, seemingly normal shadow.

---

11. Von Reuss, A.: Die Krankheiten des Neugeborenen, 1914, p. 263; Friedlander, A.: Enlargement of the Thymus Treated by the Roentgen Ray, Tr. Am. Pediat. Soc. **29**:80, 81, 1917.

EMPYEMA IN CHILDREN

WITH ANALYSIS OF ONE-HUNDRED AND SEVENTY-TWO CASES *

WILLIAM E. LADD, M.D., AND GEORGE D. CUTLER, M.D.

BOSTON

During the last three or four years, there has been a return to closed methods of drainage for empyema, with a rather more widespread adoption of these principles than on any of the previous occasions when this form of treatment had been adopted only to be discarded again partially. It is our belief that the causes of this widespread change or modification in treatment are the occurrence of streptococcus empyema in army camps, with a very high mortality attendant on rib resection, and the very prevalent misconception as to the action of the lungs in the presence of an open thorax. That there is some merit in draining pus from the chest, without leaving the pleural cavity open to the air, is apparent. From a study of the literature and an analysis of 172 of our own cases in which operation was done during what might be called this transitional period we have endeavored to ascertain what merits this form of treatment has, and to what class of cases among children it is applicable.

Every few years a paper is written emphasizing the importance of not allowing air to enter the pleural cavity in draining it and advocating some particular device for accomplishing this end. Thus Robinson devised a very clever scheme of trephining a rib and applying suction apparatus. Von Eberts devised another technic of applying suction with a Politzer bag. Holt and Remsen described still other modifications. All these methods were based on the same general principles.

In more recent years, the same principles have been advocated again with changes in the devices used. Of the more recent methods may be mentioned those of Mazingo, Phillips and Whittemore. Some clinicians advocate irrigating with surgical solution of chlorinated soda. Some apply continuous suction, others intermittent suction, but all lay claim to success partly because they do not allow air to enter the pleural cavity and partly on account of their own particular apparatus.

It is extraordinary that the belief should be so widespread that an opening in the thorax necessarily causes collapse of the lung. It would seem that almost every surgeon who has ever operated for empyema must have observed, after evacuation of the pus, how the lung expands and contracts with respiratory efforts. At times the lung comes directly to the thoracotomy opening. It likewise seems strange that

---

* Received for publication, Dec. 13, 1920.

many surgeons who perform these operations and have observed the phenomenon of the lung expanding and contracting with respiration at times and not at other times, do not ask themselves why this is so. Apparently they are contented with the statement that the lung on the affected side collapses in the presence of an open thoracotomy wound and does not in the presence of a closed wound.

In connection with these points, the experimental work of Graham and Bell is most interesting and also of great practical importance. They have shown that in the normal chest an open pneumothorax affects both sides almost equally, and that it is not until the structures of the mediastinum are held rigid, as a result of adhesions or inflammatory processes, that marked differences in the two sides of the chest occur. They also show that respiratory difficulties are dependent on the relation between the amount of air entering the thoracotomy wound and that entering the lungs. Theoretically, in a normal chest, the opening would be smaller than 2 inches by $4\frac{1}{10}$ inches to avoid respiratory embarrassment. In cases of empyema of long standing, with adhesions and a firm mediastinum, a much larger opening can be made without respiratory embarrassment ensuing. These factors make deferred operation safer than an operation done too early. This is true of all cases of empyema but particularly of streptococcus cases. It is interesting to note that at the Children's Hospital, five or six years ago, as a result of clinical experience, the same conclusion was reached which Graham and Bell have since clearly demonstrated to be true by experimental work.

Our rule, adopted at that time, was not to operate, except in the presence of frank pus and never in the presence of pneumonia. When we have not adhered to this rule consistently, we have usually regretted breaking it.

The matter of deferred operation in children is often automatically taken care of for the surgeon, through the fact that the diagnosis is considerably more difficult to make in the child than in the adult. As pointed out by Morse and Griffith, the crisis of pneumonia is less clearly defined; the physical signs are less easy to interpret and the roentgen-ray findings are often confusing. The needle must be depended on for a final diagnosis in cases of doubt. As an example of this late diagnosis in children, in our series of 172 cases, the diagnosis was made under two weeks after pneumonia in only seventy-nine cases. In eighty-five cases it was made later than two weeks after the pneumonia. In eight cases the duration was not determined. Of the seventy-nine cases, the diagnosis was made immediately after the crisis of the pneumonia only in those patients who were being treated in the hospital for their pneumonia. In many of the eighty-five cases

diagnosed over two weeks after the crisis of pneumonia, the diagnosis was frequently not made for many weeks or even months afterward. As a general rule, it may be stated that the younger the patient, the more difficult the diagnosis. Among our patients, the youngest was one month old; the eldest 12 years. There were twenty-eight patients under 2 years of age; thirty-four between 2 and 3, and the remainder between 3 and 12 years of age.

In the series there were four cases of bilateral empyema. The right pleural cavity was affected in seventy-three patients and the left in ninety-five.

Several factors enter into the question of mortality in children which cannot be defined so clearly in the adult. The age of the patient is of great significance. Nathan reports seventy-six cases under 2 years with a mortality of 78 per cent. Holt reports 127 cases with a mortality of 65 per cent., with both types of drainage. With closed drainage and siphonage he reports the slightly lower mortality of 60 per cent. In our own series there were twenty-eight cases under 2 years with a mortality of 32 per cent.

Holt reports twenty-seven cases over 2 years of age with a mortality of 16 per cent. Dowd reports 285 cases in children between the ages of 2 and 14 years with a mortality of 25.6 per cent. Our mortality in 144 cases between the ages of 2 and 12, which may be compared with his, is 13.8 per cent. Including our cases under 2 years with the others, 172 in all, the mortality is 16 per cent.

The factor of next importance to age and the condition of the patient is the type of the infection. Holt reports a mortality of 56 per cent. with pneumococcus infection; 79 per cent. with streptococcus and 50 per cent. with staphylcoccus infection.

In our cases, ninety-nine had a pneumomoccus infection, with a 12 per cent. mortality and twenty-six had a streptococcus infection with a mortality of 27 per cent. Four cases in which a pure culture of staphylococcus was obtained were without mortality. The remaining cases were either mixed infections or unknown.

It is obvious that the above facts must be considered in connection with the methods of treatment adopted. We have analyzed our series to determine the results of open or closed drainage as a whole, and also with reference to the age of the patient and the kind of infection. One hundred and fifty-four patients were subjected to rib resection. Three had double empyema. Twenty-six patients died, a mortality of a little over 16 per cent. Two of the three patients with double empyema recovered, both having both sides open at the same time. Of the 154 patients subjected to rib resection, ninety-two had a pneumococcus infection following the pneumonia. Among them twelve

deaths occurred, a mortality of about 13 per cent. Twenty-three had a streptococcus infection. Seven died, a mortality of 30.4 per cent. The four patients with a staphylococcus infection submitted to rib resection, recovered. Eighteen patients were treated by the closed method. Three died, a mortality of 16.6 per cent., a mortality identical with that in the rib resection cases. Of these eighteen patients, seven had a pneumococcus infection, with no deaths; three had a streptococcus infection, with no deaths; these eighteen patients had closed drainage; nine later required rib resection either to provide adequate drainage or to free the lung to allow expansion and obliteration of the cavity. Whereas children do not stand rough handling and hemorrhage as well as adults, the lung can be freed gently, sufficiently to allow it to expand without causing marked bleeding.

Of the 154 rib resections, 21 were done on patients under 2 years of age. Six deaths occurred, a mortality of 29 per cent. One hundred and thirty-three patients were over 2 years of age. Twenty deaths occurred, a mortality of 15 per cent. Seven patients under 2 years of age were operated on by the closed method of drainage with a mortality of 42.8 per cent. Eleven patients more than 2 years of age all survived the operation.

The question of anesthesia has not been considered enough. Ether was given to the majority of our patients. Procain and epinephrin anesthesia was used in fourteen rib resections with only one death. Although it is often impossible to do a rib resection in children under local anesthesia, it could have been used to advantage more frequently and should always be used with intercostal drainage.

The duration of convalescence with closed and open drainage seems to be the same on the average. With the closed drainage, one patient was well in a week with the wound practically healed but in the majority of cases four to five weeks elapsed as in the rib resection cases.

From this study of 172 cases, the following conclusions seem justified:

1. That in children the diagnosis frequently is not made until late: this has its influence on the type of operation to be selected.

2. That a preliminary thoracentesis should be done to ascertain the type of infection.

3. That in the streptococcus infections it is probable that aspiration or closed drainage through a tube would supply sufficient drainage and result in a lower mortality. These infections have a tendency to abort, recovery taking place without operation so that moderately good drainage will effect a cure where it would not in other types of cases.

4. That in cases of pneumococcus empyema, closed drainage is useful as a temporary measure in the case of the extremely sick patients but it is not to be recommended as the operation of choice. It does not supply adequate drainage and it does not allow the operator to free the lung, which can be done in a child through a small opening with one finger. This is a routine procedure with us and has a great deal to do with our scarcity of chronic cases. We would agree with Dowd that "if the lung expands at the time of operation, suction is not needed, and if it does not, suction will probably not make it."

5. That the causes of so-called collapsed lung is not the presence of atmospheric pressure through an open wound, but the result of inadequate operation and drainage. That in the few patients in whom it is unwise to free the lung at the first operation and in whom the lung remains bound down by adhesions, a decortication is required. This, in our experience, is always sufficient to obliterate the cavity and cause healing.

6. That operations causing collapse of the chest wall, as recommended by Estlander and Schede, are contraindicated because they cause distressing deformities and are unnecessary.

7. That there are certain definite indications for closed drainage and suction and this form of treatment should be limited to such cases only.

In conclusion, we would emphasize Hartwell's statement that, "no form of treatment for empyema which disregards the thorough drainage of the chest by a rib resection and the gradual re-expansion of the lung by respiratory efforts, meets the requirements."

BIBLIOGRAPHY

Holt, L. E.: Siphon Treatment of Empyema in Infants and Young Children, J. A. M. A. **61**:381 (June) 1913.

Graham and Bell: Am. J. M. Sc. **156**:839, 1918.

Robinson, S.: Boston M. & S. J., October, 1910.

Von Eberts, E. M.: J. A. M. A. **59**:264 (July 27) 1912.

Griffith, J. P. C.: The Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1919.

Nathan: Arch. f. Kinderh. **36**:252, 1903.

Remsen, C. M.: J. A. M. A. **59**:1712 (Nov. 9) 1912.

Dowd, C. N.: New York State J. M. **14**:339 (July) 1914.

Moore, J. L.: Diagnosis of Metapneumonic Empyema in Infancy and Early Childhood, Am. Med. **7**:430 (March 12) 1904.

Gage, H.: Empyema, Boston M. & S. J. **181**:84 (July 24) 1919.

Churchill, F. S.: Empyema in Children, with Special Reference to Diagnosis, Boston M. & S. J. **181**:87 (July 24) 1919.

Lilienthal, H.: Thoracic Fistula and Chronic Empyema, Ann. Surg. **70**:43 (July) 1919.

Rodman, J. S.: Empyema, Ann. Surg. **70**:49 (July) 1919.

Hartwell, J. A.: Treatment of Empyema, Ann. Surg. **70**:55 (July) 1919.

Whittemore, W.: The Surgical Treatment of Acute Empyema Following Influenza, Boston M. & S. J. **181**:692 (Dec. 11) 1919.

CHANGES IN THE FORM AND DIMENSIONS OF THE CHEST AT BIRTH AND IN THE NEONATAL PERIOD *

RICHARD E. SCAMMON, Ph.D., and WILLIAM H. RUCKER, B.S.

MINNEAPOLIS

In the fortnight following birth, the form and dimensions of the thorax undergo a series of peculiar changes which are dependent on a number of different factors. One of these changes, the increase in the horizontal circumference of the chest accompanying the first inspiration, is well known, but others, which are less marked and more variable, have apparently passed unnoticed. The following account of the changes in the form of the thorax of the new-born is based on measurements of the thoraces of late fetuses and full term still-born children, on observations of living infants on the first, third, fifth, seventh, tenth and twelfth days after birth, and on a number of observations on the horizontal chest circumference immediately before and after the first inspiration. The observations on the dimensions of the fetal thorax were made by Dr. L. A. Calkins as a part of an extensive study on the development of the proportions of the body in prenatal life, and our thanks are due him for permission to use these valuable data in the present investigations. The study on living infants was made at the Minneapolis General Hospital. In our study it proved impracticable to make thoracic measurements of the new-born until ten or fifteen minutes after birth and we have, therefore, made use of the excellent series of observations of Linzenmeier for data on the circumference of the chest immediately before and after the first inspiration.

Changes in the Horizontal Chest Circumference.—The horizontal circumference of the chest is usually determined at the level of the nipples, at the level of the lower end of the sternum, or at the tenth rib. Our study was based on measurements at the nipples and at the tenth rib. As the results of these measurements are not identical they will be considered separately.

The changes in the chest circumference at the level of the nipples are shown in Table 1 and in graphic form in Figures 1, 2 and 3. They are best presented by Figure 1, which is a semischematic curve show-

ing the entire series of modifications in this dimension from late fetal life until the close of the second week after birth. Four phases may be recognized in this curve. The first phase, which includes the latter part of fetal life, is characterized by a slow increase in chest circumference directly proportional to the growth of the body in length and without any marked changes in rate of growth. The second phase is inaugurated with the first inspiration. Within the first few minutes after birth, and often with the first breath, the chest cicumference increases about 2 cm., or approximately 8 per cent. This period of rapid increase is a transitory one for, as a rule, before the close of the first twelve hours a third phase, one of circumference decrease, begins and this continues for two or three days thereafter. The final phase, one of circumference recovery, sets in on the third or fourth day, and by the latter half of the second week the thorax has regained the circumference which obtains immediately after the first inspiration.

TABLE 1.—Changes in the Horizontal Circumference of the Chest (at the Level of the Nipples) at Birth and in the Neonatal Period

Age	Number of Cases	Average Circumference, Cm.	Average Circumference in Per Cent. of the Chest Circumference 15 Min. after Birth
Birth (before first inspiration)	40	29.3*	88.9
15 minutes after birth.........	36	31.2	100.0
12 hours after birth...........	36	30.7	92.8
3d day after birth.............	36	29.7	97.1
5th day after birth............	34	30.2	97.7
7th day after birth............	31	30.3	98.0
10th day after birth...........	19	30.5	98.8
12th day after birth...........	6	31.2	100.8

* Calculated from the data of Linzenmeier.

The modifications in the circumference of the chest at the level of the tenth rib are shown in Table 2 and in Figures 2 and 3. In later fetal life the circumference at this level, like that at the nipples, increases slowly and steadily at a rate directly proportional to the growth of the body in length. We have no direct data on the changes in the tenth rib circumference with the establishment of respiration, but judging from the changes in the diameters of the chest at this level, there is some increase in circumference although not as much as at the level of the nipples. The later postnatal changes in the tenth rib circumference are very similar to those in the nipple circumference. From the first to the fourth or fifth day, there is a period of circumference decrease. This is followed by a second period of slow increase, the initial circumference following the establishment of respiration being regained about the tenth or twelfth day (Fig. 2).

The postnatal decrease in chest circumference does not seem to have been observed previously. This is not surprising, for the loss is generally

small and would hardly be noticed unless systematic measurements were made day by day throughout the neonatal period on a considerable series of cases. The variability in the horizontal chest circumference at birth is considerable. Taylor [2] found that the standard deviation of the circumference at the nipples was 12.2 mm. for males and 17.7 mm. for females. With this degree of variation it is probable that the postnatal decrease would be entirely masked in any series of measurements taken at random at birth and in the neonatal period. While the reduction in chest circumference is often small, it seems to be fairly constant. Our measurements show some reduction at the level of the nipples in thirty-three of the thirty-six cases studied, and at the tenth rib in thirty-
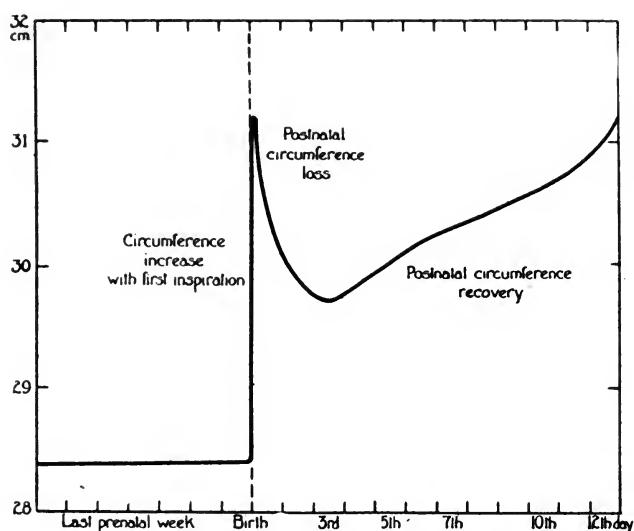
Fig. 1.—A semischematic curve illustrating the changes in the absolute circumference of the chest, at the level of the nipples, at birth, and in the first twelve days of postnatal life. Based on measurements of fetuses and still-born children and on observations on a series of living infants.

four cases. As is indicated in Tables 3 and 4, the variability in the amount of postnatal reduction is very great. The time of maximum reduction also differs considerably in various cases.

Since there is considerable individual variation in the circumference of the chest at birth, we have attempted to check the results of our absolute measurements by reducing these determinations to a percentage basis. This we have done by considering the circumference of the chest immediately after the establishment of respiration as 100 and calculating all later measurements as percentages of this initial one. This cal-

2. Taylor, R.: The Measurements of Two Hundred and Fifty Full-Term New-Born Infants, Am. J. Dis. Child. **27**:353 (April) 1919.

culation was first made for each case separately and the individual percentages for each period of observation were then averaged. This procedure eliminates much of the error which is introduced in the average absolute dimensions by initial differences in size of the individual cases. The results of these calculations are given in the fourth columns of Tables 1 and 2 and are illustrated by the curves in Figure 3. These figures on the *percentage* loss and gain of the chest circumference in the neonatal period differ slightly from those obtained from the averages of the absolute dimensions, but the general courses of the changes as determined by these two methods are in close agreement.

The causes of these changes in chest circumference seem to be diverse. The increase in the later part of fetal life reflects the general growth of the tissues and organs of the thorax and probably, in particular, the formation of new lung alveoli, which is very active in this period. The sudden increase at birth no doubt corresponds, in the main, to the initial enlargement of the thorax which takes place at the establishment of respiration and which is accompanied by the partial

TABLE 2.—CHANGES IN THE HORIZONTAL CHEST CIRCUMFERENCE (AT THE LEVEL OF THE TENTH RIB) IN THE NEONATAL PERIOD

Age	Number of Cases	Average Circumference, Cm.	Average Circumference in Per Cent. of the Chest Girth Immediately after Birth
15 minutes after birth.........	36	31.4	100.0
12 hours after birth............	36	30.5	97.4
3d day after birth.............	36	29.5	96.6
5th day after birth............	34	30.5	96.8
7th day after birth............	31	30.8	97.8
10th day after birth...........	17	30.7	97.6
12th day after birth...........	11	31.0	100.9

expansion of the lung alveoli. It is possible that the dilation of the vascular bed of the lungs, following the close of the ductus arteriosus and the complete establishment of the pulmonary circulation, is also represented in this increase. The postnatal loss in circumference, on the other hand, seems to have nothing to do with the expansion of the lungs. In all probability, it is to be interpreted as another manifestation of the postnatal loss in mass of the infant, and, particularly, as an indication of the loss of fluid from the superficial tissues of the chest wall.

The changes following the phase of postnatal circumference decrease seem dependent on several factors. The enlargement of the thorax with the completion of the expansion of the lungs is probably the most important of these. The studies of a number of observers, and, particularly, the extensive observations of Gedgovd [3] have shown that all parts of the lungs are not fully expanded at the first inspiration or

3. Gedgovd, V. A.: Anatomical Peculiarities of the Respiratory Organs in Childhood. Diss. St. Petersburg, 1900.

even in the first few days, but that it is often a week or more before all of the alveoli are even partially dilated. And the investigations of Ridella,[4] as well as the older data of de la Croix [5] and Rossignol [6] indicate that this initial dilatation of the alveoli is not a complete one. These conclusions are supported by the careful micrometric studies on the lungs of fetal and new1born animals by Addison and Howe.[7] It seems, then, that the volume of the lungs (and, therefore, the internal dimensions of the thorax) are normally increasing throughout the neonatal period, but that the effect of this increase on the external dimensions of the thorax is obscured in the first few days after birth by the more extensive decrease in the superficial soft parts of the chest wall which
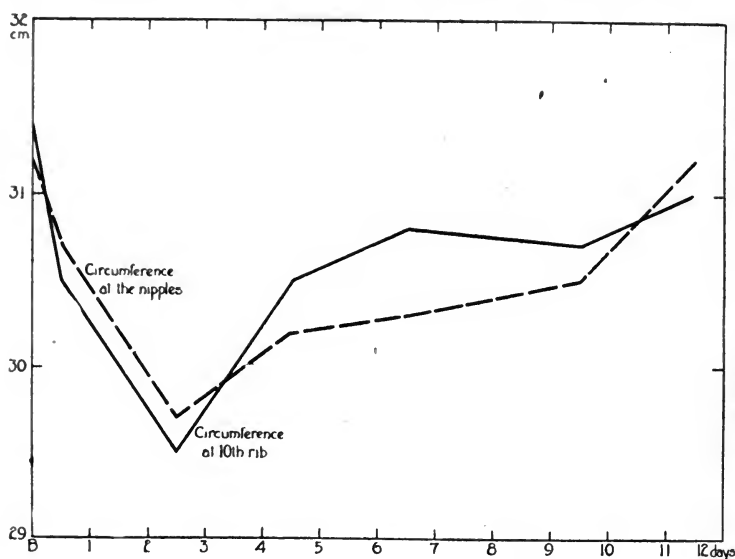
Fig. 2.—A graph illustrating the changes in absolute chest circumference, at the nipples and at the tenth rib, in the first twelve days of postnatal life. Based on measurements of a series of thirty-six children.

is associated with the postnatal weight loss. The effect of the continued increase in the volume of the lungs and thoracic cavity is pictured in the rise of the curve of the chest circumference which occurs in the latter part of the neonatal period after the major portion of the post-

4. Ridella, A.: Modificazioni che avvengo nel polmone prima o dopo la nascita in relazione colla funzione respiratoria, Folia Gynaecol. 7:421, 1912.

5. de la Croix, N. J.: Die Entwicklung des Lungenepithels beim menschlichen Fötus und der Einfluss der Atmung auf Dasselbe, Arch. f. mikr. Anat. 22:93, 1883.

6. Rossignol: Recherches sur la structure intime du pulmon de l'homme, Thèse, Bruxelles, 1846.

7. Addison, W. H. F., and Howe, H. W.: On the Prenatal and Neonatal Lung, Am. J. Anat. 15:199, 1913.

natal weight decrease has taken place or when the recovery in body weight begins. A comparison of the changes in chest circumference with those in body weight in certain of our cases seems to support this view, for we find that the circumference loss and body weight loss are often synchronous while the recovery of the initial chest circumference often does not coincide with the recovery in body weight, but takes place a little sooner or even while the body weight is stationary. Other minor factors, such as the enlargement of the mammary glands associated with the formation of "witches' milk," may also have a slight effect on the circumference at the nipples.

TABLE 3.—EXTENT OF POSTNATAL LOSS IN CHEST CIRCUMFERENCE AT THE LEVEL OF THE NIPPLES. (CALCULATED IN PER CENT. OF THE CHEST CIRCUMFERENCE 15 MINUTES AFTER BIRTH.)

	Number	Per Cent.
Cases showing no loss in circumference..........................	3	9
Cases showing a loss of less than 5 per cent.	14	39
Cases showing a loss of 5 to 10 per cent.	14	39
Cases showing a loss of 10 to 15 per cent.	4	11
Cases showing a loss of 15 per cent. or more.................	1	2

The postnatal changes in the circumference at the tenth rib are probably due, in the main, to the same factors which influence the circumference at the nipples. The neonatal reduction at the tenth rib is a little greater and the recovery a little slower than at the nipples, presumably because the enlargement of the lower part of the chest in con-

TABLE 4.—EXTENT OF POSTNATAL LOSS IN CHEST CIRCUMFERENCE AT THE LEVEL OF THE TENTH RIB. (CALCULATED IN PER CENT. OF THE CHEST CIRCUMFERENCE 15 MINUTES AFTER BIRTH.)

	Number	Per Cent.
Cases showing no loss in circumference..........................	2	6
Cases showing a loss of less than 5 per cent.	10	27
Cases showing a loss of 5 to 10 per cent.	20	56
Cases showing a loss of 10 to 15 per cent.	4	11

nection with the expansion of the lungs is less marked. Another factor which may play a part in the reduction of the tenth rib circumference is the postnatal decrease in the size of the liver which has been described by Miura.[8] This author finds a decline in the mass of the liver after birth which may be attributed to the decrease in blood content of the liver following the interruption of the flow of placental blood to the organ with the closure of the umbilical vein.

Changes in the Diameters of the Chest.—The anteroposterior and transverse diameters of the thorax were measured at the nipples and at

---

8. Miura, M.: Die Gewichtsabnahme verschiedener Organe vom Neugeborenen, Notizen meiner physiologischen und pathologischen Forschung, No. 15, 1912.

the tenth rib in our series of living children. The summarized results of these measurements are shown in Tables 5, 6, and 7 and are represented graphically by the curves in Figures 4 and 5.

The changes in the diameters of the chest at the level of the nipples and at the tenth rib are quite similar in the neonatal period. After breathing begins the anteroposterior and transverse diameters undergo a series of modifications in which three main phases may be recognized. Of these the first is a period of diameter decrease which begins after respiration is established and extends from twelve hours to three or four days thereafter. The second phase occupies the latter part of the first week and the beginning of the second. During this time the diameters
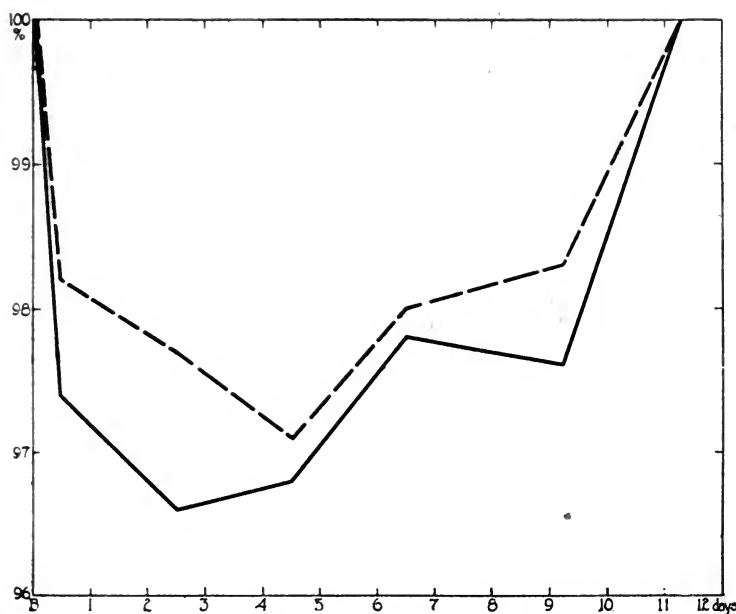
Fig. 3.—A graph illustrating the changes in the circumference of the chest at the level of the nipples and the level of the tenth rib. The circumferences for the first and later days are calculated in per cent. of the circumference of the chest ten to fifteen minutes after birth.

may decline slightly, remain stationary, or show minor fluctuations which are probably without significance. In the third period, which falls in the middle or latter part of the second week, the diameters again begin to increase and their initial dimensions (as observed immediately after the establishment of respiration) are generally regained between the tenth and fourteenth day. Thus the changes in the diameters of the thorax in the neonatal period show the same general characters of postnatal loss and recovery which were found in connection with the circumferences of the chest.

The postnatal reduction in the diameters of the chest is a fairly constant phenomenon. The anteroposterior diameter at the nipples showed a reduction in twenty-two of the twenty-three cases studied, and the transverse diameters in twenty cases. At the tenth rib the anteroposterior diameter was reduced in eighteen of twenty-three cases and the transverse diameter in twenty-two cases. The amount of reduction of the anteroposterior diameters is much greater both absolutely and relatively than the reduction of the transverse diameters. This is true of the diameters both at the level of the nipples and at the tenth rib. This difference, as well as the variation in reduction in individual cases, is shown in Tables 6 and 7. The causes of these changes will be considered in connection with the thoracic index.

Changes in the Thoracic Index.—The thoracic index is a value determined by dividing the anteroposterior diameter of the chest by the transverse diameter and multiplying the quotient by 100. The result

TABLE 5.—Changes in the Diameters of the Chest in the Neonatal Period

Age	Number of Cases	Average Diameters at the Nipples		Average Diameters at the Tenth Rib	
		Transverse	Antero-posterior	Transverse	Antero-posterior
15 minutes after birth...............	23	7.7	8.2	8.9	8.5
12 hours after birth..................	23	7.7	7.9	8.7	8.0
3d day after birth....................	23	7.5	7.7	8.8	7.9
5th day after birth...................	21	7.5	7.6	8.6	7.8
7th day after birth...................	18	7.5	7.7	8.8	8.0
10th to 12th days after birth........	10	7.7	7.8	8.9	8.1

gives the anteroposterior diameter of the thorax in the form of a per cent. of the transverse diameter, and is an expression of the relative depth of the chest. Thanks to the studies of Hutchinson,[9] Mehnert,[10] Rodes,[11] Jackson[12] and others the general course of the changes in the thoracic index in the developmental period is well known. It is very high (nearly 200) in the young embryo because of the large size and great anteroposterior diameter of the heart and liver; but with the development of the thoracic skeleton it gradually falls to less than 90 in the fetus at term. In childhood the index continues to decline, usually falling to about 70 in maturity. The index is markedly affected at birth by a number of factors. The course of the modifications of the

9. Hutchinson, W.: Some Deformities of the Chest in the Light of Its Ancestry and Growth, J. A. M. A. **29**:512, 1897.

10. Mehnert, E.: Ueber topographische Altersveränderungen des Atmungsapparates, Jena, 1901.

11. Rodes, C. B.: The Thoracic Index in the Negro, Ztschr. f. Morphol. u. Anthropol. **9**:102, 1906.

12. Jackson, C. M.: Is Gravity the Factor Determining the Thoracic Index? Ztschr. f. Morphol. u. Anthropol. **10**:240, 1907.

thoracic index at the nipples in the neonatal period is shown in Table 8 and by Figure 6.

The changes in the index at the level of the nipples are shown in semischematic form in curve B of Figure 6. In the latter part of fetal life (ninth and tenth fetal months) the average index is about 86.[13]
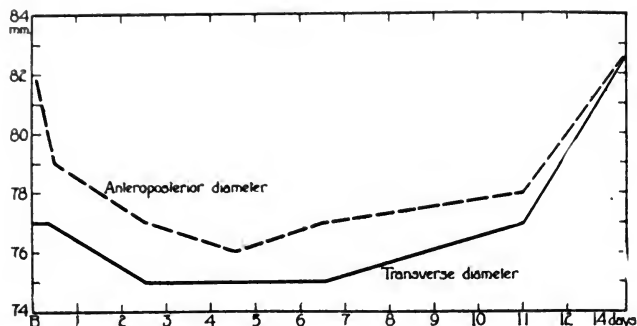
Fig. 4.—A graph illustrating the changes in the anteroposterior and transverse diameters of the chest, at the nipples, in the first twelve days after birth.
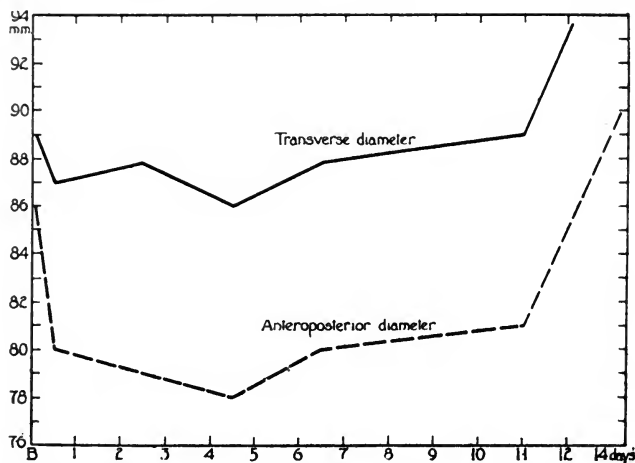
Fig. 5.—A graph illustrating the changes in the anteroposterior and transverse diameters of the chest at the tenth rib, in the first twelve days after birth.

At birth, with the establishment of respiration, it rises immediately to an average of 106. This initial rise is followed almost at once by a rapid decline, the index falling to an average of 102 within twelve hours after birth. During the remainder of the neonatal period, the measure drops

13. This determination was made from Dr. Calkins' material and is not corrected for the changes which occur in the chest on injecting the cadaver. Dr. Calkins' observations show that these changes tend to increase the anteroposterior diameter more than the transverse, and that the true thoracic index in later fetal life is a little lower than is here recorded.

slowly and irregularly, being about 100.5 in the middle of the second postnatal week. Six months or more pass before it has declined to the average which obtains just before birth.

The changes in the index at the level of the tenth rib are similar in character but are less pronounced than those at the level of the nipple. They are presented semidiagrammatically by curve A of Figure 6. In the latter part of fetal life and in children who have not breathed, the average index at the lower level is 91 or 92. With the establishment of respiration, it rises to an average of 95 and then declines again, in the course of the first twenty-four hours, to 92. By the middle of the second postnatal week it has dropped to 86.

TABLE 6.—EXTENT OF POSTNATAL LOSS IN THE TRANSVERSE AND ANTERO-POSTERIOR DIAMETERS OF THE CHEST AT THE LEVEL OF THE NIPPLES

	Antero-posterior Diameter	Trans-verse Diameter
Number of cases showing no reduction....................................	1	3
Number of cases showing a reduction of less than 0.5 cm.	1	8
Number of cases showing a reduction of between 0.5 and 1.0 cm.	9	8
Number of cases showing a reduction of between 1.0 and 1.5 cm.	11	4
Number of cases showing a reduction of between 1.5 and 2.0 cm.	1	0

The rise in the thoracic index which occurs immediately after birth presumably takes place at the first breath when the chest wall is carried upward and forward as in the inspiratory movements of later life. The causes of the decline of the index which follows this initial rise are more obscure. We are inclined to attribute the change, in part at least, to the effect of gravity on the form of the chest. During prenatal life the fetus

TABLE 7.—EXTENT OF POSTNATAL LOSS IN THE TRANSVERSE AND ANTERO-POSTERIOR DIAMETERS OF THE CHEST AT THE LEVEL OF THE TENTH RIB

	Antero-posterior Diameter	Trans-verse Diameter
Number of cases showing no reduction..	1	5
Number of cases showing a reduction of less than 0.5 cm.	2	8
Number of cases showing a reduction of between 0.5 and 1.0 cm.	8	5
Number of cases showing a reduction of between 1.0 and 1.5 cm.	9	4
Number of cases showing a reduction of between 1.5 and 2.0 cm.	3	1

is surrounded with fluid' and consequently all external pressures are transmitted to its surfaces equally from all sides. Thus the tendency of all external pressures would be to mold the body into spherical form of which all diameters would be equal. But after birth, when the infant spends the greater part of the time prone on the back or abdomen, the force of gravity would be exerted on the anterior or posterior surfaces of the thorax, tending to decrease its anteroposterior diameter and to increase its transverse diameter. While it seems reasonable to regard

gravity as one of the important factors in the early reduction of the thoracic index, it is probable that the modifications in the forms of the chest which are due to this factor take place in a comparatively short time after birth.   Jackson's experiments [12] indicate that gravity has little to do with the slow flattening of the chest which goes on in later infancy and childhood.

It is possible also that the dropping of the dome of the diaphragm after birth may have some effect on the thoracic index.   That the
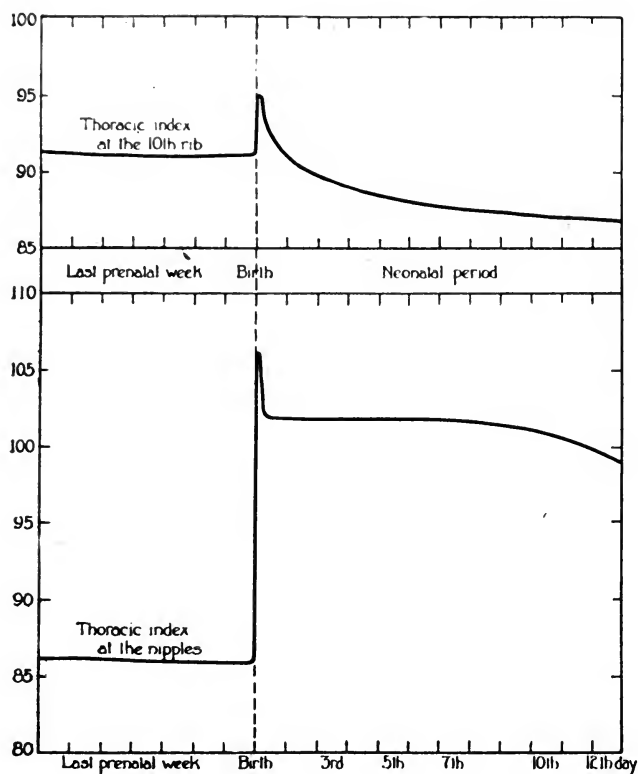
Fig. 6.—Two semischematic graphs illustrating the changes in the thoracic index at birth and in the neonatal period.

diaphragm does descend in the thorax shortly after birth seems well established, but so little is known either of the extent or the time of this change that it is hardly possible to correlate it with the modifications in chest form.

Whatever factors may be responsible for the modifications in the thoracic index in the neonatal period, these changes are correlated in an interesting manner with the internal changes of the lungs.   It was

pointed out by Champneys [13] a number of years ago that the inflation of the lungs does not take place at the same rate in all parts of these organs. He found that the anterior surfaces and medial margins were expanded distinctly before the lateral portions and the inferior margins.[15] Thus the early expansion of the anterior surfaces and medial margins of the lungs reflects the early increase in the anteroposterior diameter of the thorax, particularly at the level of the nipples, while the subsequent expansion of the lateral portions corresponds to the later increase in the transverse diameters. And, similarly, the expansion of the lower portions and inferior margins is considerably delayed in correspondence with the slower and smaller changes in the circumference and thoracic index at the level of the tenth rib.

SUMMARY

At birth and in the neonatal period the thorax undergoes a series of modifications in dimensions and form which may be summarized as follows:

TABLE 8.—CHANGES IN THE THORACIC INDEX AT BIRTH AND IN THE NEONATAL PERIOD

Age	Number of Cases	Average of Indices	
		At the Level of the Nipples	At the Level of the Tenth Rib
9th fetal month.............................	18	86.5	92
10th fetal month............................	13	86.0	92
Birth (full-term fetuses)...................	19	86.0	91
15 minutes after birth......................	23	106.0	95
1st day (12 hours) after birth..............	23	102.0	92
3d day after birth..........................	23	102.0	89
5th day after birth.........................	21	100.5	91
7th day after birth.........................	18	102.0	91
10th and 12th days after birth.............	10	100.5	88

1. The horizontal chest circumference (at the nipples) is markedly increased at the first inspiration. In the first day, within twelve hours after birth, it enters a period of decrease which continues for two or three days and which is followed by a period of circumference increase. The initial circumference following the first inspiration is regained in the second week.

2. No data are available as to the changes in the circumference of the chest at the tenth rib with the establishment of respiration, although it is probable that they are somewhat similar to those at the nipples,

14. Champneys, F. H.: Second Communication on Artificial Respiration in Still-Born Children. The Expansibility of the Various Parts of the Lungs, Medico-Chir. Trans., Ser. 2 **42**:87, 1881.

15. These findings are substantially confirmed by G. J. Noback, working in this laboratory, who has investigated the condition of the thoracic viscera of the new-born both in the fresh condition and after intravascular fixation. His results will be published separately.

although less extensive. After respiration is established, the circumference at the tenth rib undergoes, first, a decrease, and then an increase, in a manner similar to that of the circumference at the level of the nipples.

3. The anteroposterior and the transverse diameters of the thorax, both at the level of the nipples and at the level of the tenth rib, show changes comparable with those of the circumferences at these levels. They decline in magnitude from the first to the fifth day after birth, and then enter a period of recovery, the initial dimensions (after respiration is established) being regained about the middle of the second postnatal week. The anteroposterior diameters undergo a much greater reduction than the transverse diameters.

4. The thoracic index at the nipples stands at about 86 before birth. With the establishment of respiration it rises to an average of 106 and then drops to about 102 in the first twenty-four hours. During the remainder of the neonatal period, it declines irregularly and slowly, being 100.5 in the middle of the second week. The changes in the thoracic index at the level of the tenth rib are of the same general character as those at the level of the nipples but are less pronounced.

5. The changes in the form and dimensions of the chest in the neonatal period (with the exception of the postnatal loss in circumference and diameter which seem to be associated with postnatal weight loss) are reflected in the order and degree of expansion of the different parts of the lungs.

THE ABSORPTION OF FLUID INJECTED INTO THE PERITONEAL CAVITY *

B. S. DENZER, M.D., and A. F. ANDERSON, M.D.

NEW YORK

Intraperitoneal injection is one of the accepted methods of parenteral administration of fluid. In conditions such as diarrhea, in which dehydration is extreme, repeated administration of fluid is often necessary—under the skin, into the veins and into the peritoneal cavity. The question of the absorption of fluid by the peritoneum is, therefore, a matter of very practical import.

Postmortem examination of infants that received fluid intraperitoneally a short time before death, has already thrown some light on the problem of absorption. Blackfan and Maxcy[1] conclude that absorption is rapid. They record the recovery of 20 c.c. of fluid in an infant weighing 20 pounds, that received 250 c.c. eighteen hours, and 200 c.c. six hours before death. The fluid was clear yellow; the peritoneum was glistening and no mention was made of deposition of fibrin, cellular exudate or other evidence of inflammatory reaction.

Our own necropsy findings indicate varying rates of absorption. (Table 1). In several cases, large amounts of fluid injected within thirty hours before death were completely absorbed; occasionally fluid was present at necropsy several days after injection, and in two cases fibrin was found in the iliac fossae. As a rule, all but a comparatively small amount of the injected fluid was absorbed at the end of twenty-four hours.

The use of capillary needles for abdominal puncture described recently[2] provided a method of tracing the reaction to and the absorption of injected fluids. During the course of the work the technic and instruments were modified.

The original method consisted in the use of a metal needle to puncture the skin, and inserting through the opening thus made a glass capillary needle. To obviate the disadvantage of using glass needles, metal cannulas and glass capillary tubes were devised. Only the latest and thus far the most satisfactory type will be described.

The instrument consists of a trocar-cannula[3] and glass capillary tubing and is shown in Figure 1. The cannula is conveniently held

1. Blackfan and Maxcy: Am. J. Dis. Child. **15**:19 (Jan.) 1918.

2. Denzer: Am. J. Dis. Child. **20**:113 (Aug.) 1920.

3. The instruments were made for us by the Randall Faichney Co. of Boston.

by handles on either side. The shoulder is as short as it can be made, and is so constructed that on removal of the trocar it will take a Luer syringe or a Luer adapter. The object of this is to permit the injection of saline solution following the test puncture for the presence of fluid. The shaft of the cannula is 17 gage and one half inch in length. The point of the cannula is made in two forms (Fig. 1 A). One is blunt; therefore the trocar is sharp and bevelled in the form of a spear

TABLE 1.—Postmortem Findings in Ten Cases in Which Fluid Was Injected Into the Peritoneal Cavity

Name	Age	Weight Lbs. Oz.	Diagnosis	Amount Injected, C.c.	Interval Between Injection and Death	Amount of Peritoneal Fluid Found Postmortem, C.c.	Remarks
Stanley G. ...	5 mos.	13 ..	Acute intestinal intoxication	150	2 hrs.	60	Turbid fluid; plaques of epithelial cells; many degenerated
L. S.	5 mos.	11 ..	Acute intestinal intoxication	250	1½ hrs.	150	
John T.	7 mos.	10 ..	Acute intestinal intoxication	150 ·	20 hrs.	½	16,000 cells per c.mm.; lymphocytes predominant; many degenerated
Walter F. ...	13 mos.	18 ..	Pneumonia	200	16 hrs.	18	Yellow turbid fluid
Jane C.	8 mos.	17 5	Acute intestinal intoxication	275 250	30 hrs. 16 hrs.	none	
Julia M.	5 wks.	4 8	Pneumonia	125	40 hrs.	none	
Dalton D. ...	3 mos.	6 ..	Acute intestinal intoxication	100	28 hrs.	none	
Wm. W.	10 wks.	7 4	Acute intestinal intoxication, bronchopneumonia	130	4 days	4	
Henry B.	3 mos.	6 ..	Acute intestinal intoxication	100 125	53 hrs. 34 hrs.	15	Intestinal coils edematous, covered with sticky mucoid material; 2 pieces yellowish fibrin 2.5 cm. long in iliac fossa
Catherine S.	2 mos.	6 ..	Acute intestinal intoxication, bronchopneumonia	175	69 hrs.	4	Few flakes of fibrin in iliac fossa

head. This type of trocar-cannula requires more pressure to insert it through the abdominal wall, but on removal of the trocar, it has the advantage—possibly only theoretical—of presenting a flat surface to the intestinal coils. The second form of cannula has a sharp bevelled tip (Fig. 1 B), and the point of the trocar is made to correspond. The advantage of this form of cannula is its easy insertion through the abdominal wall; and an objection—possibly only theoretical—is that it presents a sharp point to the intestinal coils.

Most of the capillary tubes were prepared by us from tubing about 4 mm. in diameter. This tubing was drawn out in the Bunsen flame and, naturally, varied in thickness. Only those parts were used that accurately fitted the shoulder or rather the proximal part of the shaft, and the tubing was cut off so as to protrude 1 or 2 mm. from the tip of the cannula. The purpose of this technic is to prevent the breaking of the capillary tube within the peritoneal cavity. The cannula with the capillary tube prepared in this way is illustrated in Figure 1 C. The capillary tube impinges on the wall of the cannula at (a). After the tubing is safely inserted into the cannula, a break, if it occurs at all, will take place above the point—(a) and the lower fragment, firmly fixed in the shaft, can be withdrawn with the cannula. During the latter part of this study, capillary tubing was prepared by glass blowers (Fig. 1 D).
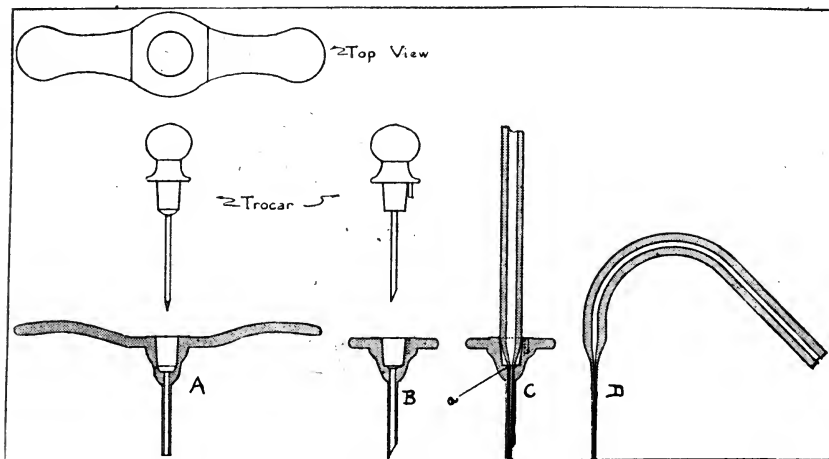
Fig. 1 (Drawn to scale and double the actual size).—A. Cannula with blunt tip and trocar with spear head point. B. Cannula and trocar with bevelled point. C. Cross section of cannula with tubing in place. Tubing is firmly fixed in the cannula at *a*. D. Tubing drawn out by glass blowers.

When glass tubing was used repeatedly, the utmost precautions were necessary to obtain clean surfaces. As capillarity depends on the capacity of the liquid to moisten the surface of the tube, a minute film of fatty material might check the rising column of fluid. Cleaning fluid, hot water, alcohol and ether were used in obtaining clean glass ware.

The technic with the trocar-cannula and capillary tube is as follows: After sterilization of the skin and the usual precautions to determine bladder distention, the trocar-cannula is inserted; the sudden release of pressure indicates that the peritoneal cavity has been entered. The

trocar is then removed, and the capillary tube is inserted as far as it will go. It is advisable to wait a few moments and to turn the needle in various directions before concluding that there is no fluid. Possibly, a bit of omentum or the wall of the intestine may temporarily block the capillary tube; or when there is only a small amount of fluid, this momentary wait and the straining and crying of the infant

TABLE 2.—RESULTS OF ABDOMINAL TAP IN CASES NOT RECEIVING INTRAPERITONEAL INJECTIONS OF FLUID

Name	Age	Weight, Lbs. Oz.		Diagnosis	Result of Tap*
Dalton D.	10 weeks	6	11	Intoxication......................	0
Wm. N.	4 months	9	6	Intoxication......................	0
Thos. B.	3 months	6	..	Intoxication......................	0
Edward D.	10 weeks	6	10	Intoxication......................	0
Veronica H.	10 months	13	8	Intoxication......................	0
Margaret C.	8 months	15	6	Intoxication......................	0
Wm. J.	8 months	12	2	Tuberculosis......................	0
Baby Gon.	3 weeks	6	6	Septicemia........................	0
Gordon G.	10 months	12	∴	Malnutrition (distention).......	0
Daniel..............	4 weeks	6	..	Malnutrition......................	0
Wm. W.	3 weeks	6	..	Malnutrition......................	0
James B.	3 months	6	2	Marasmus.........................	0
Mary S.	3 months	8	..	Intoxication......................	0
Raymond A.	8 months	10	14	Marasmus.........................	0
John G.	6 months	13	..	Intestinal indigestion...........	0
Drouet.............	4 months	..	..	Marasmus.........................	0
Marie C.	4 weeks	6	8	Intestinal indigestion...........	0
Paulo R.	2 months	8	12	Intoxication, marasmus.........	0
Frank S.	11 weeks	..	..	Marasmus.........................	0
LeRoy C.	4 weeks	8	1	Intestinal indigestion, syphilis..	0
Mary C.	5 months	7	2	Intestinal indigestion...........	0
Madeleine E.	4 months	7	4	Intestinal indigestion...........	0
John M.	10 weeks	5	6	Marasmus.........................	0
Hannah R.	10 weeks	8	4	Malnutrition......................	0
Stewart S.	5 months	11	8	Rickets...........................	0
William W.	5 months	12	6	Rickets...........................	0
Susan H.	4 months	8	2	Tuberculosis......................	0
Lucinda P.	3 months	5	8	Marasmus.........................	0
Dominick D.	5 months	9	8	Pneumonia........................	0
Martha L.	4 months	9	..	Malnutrition......................	0
Richard P.	10 weeks	5	12	Malnutrition......................	0
John S.	5 months	8	13	Intoxication......................	0
Virginia K.	4 months	4	..	Marasmus.........................	0
John R.	4 months	11	8	Intoxication......................	0
Agnes H.	3 months	6	..	Marasmus.........................	+
Joseph W.	18 months	11	2	Marasmus, tuberculosis.........	+
James P.	3 months	5	8	Marasmus.........................	+
Joseph B.	7 months	5	14	Marasmus.........................	+
Marie O'D.	6 months	8	8	Rickets...........................	+
Isaac S.	11 months	14	14	Rickets...........................	+
Lloyd L.	8 months	9	13	Rickets...........................	+
Leon T.	4 months	9	12	Rickets...........	+
Herman B.	6 months	16	..	Rickets, tuberculosis............	+
Edward T.	3 years	..	..	Peritonitis, tuberculosis.........	+
Baby L..............	2 months	6	6	Peritonitis........................	+
Pietro V.	2 months	10	..	Empyema, peritonitis...........	+
Beatrice J.	....	..	..	Tuberculosis......................	+
May S.	....	..	..	Tuberculosis......................	+
Hugh R.	14 months	14	12	Tuberculosis......................	+
Baby H.	....	..	..	Cirrhosis luetic..................	+

* 0 = dry tap, + = fluid obtained.

may aid in distributing it over the entire peritoneal cavity. At any rate, the sight of the gradually rising column of fluid has frequently rewarded this precaution. If the tap is dry and an injection of saline solution is indicated, it may be given through the cannula. Any place on the abdomen, except those parts covering a solid viscus or one

fixed by a short mesentery, may be used. As a rule, punctures were made a short distance below the umbilicus in the midline.

Abdominal taps have been made in fifty cases (Table 2). In thirty-four cases no fluid was obtained. The sixteen cases which showed fluid comprised three cases of generalized tuberculosis, one of acites with congenital syphilis, three of peritonitis, four of marasmus and five of rickets with pot belly.[4] We may conclude, then, that in the normal peritoneal cavity no free fluid can be demonstrated by the method employed by us.

It was important to determine whether fluid can be obtained with the capillary tube only when there is a large ascites or whether this method can demonstrate very minute quantities. The effort was, therefore, made to reproduce a very small peritoneal effusion and then to recover some of the fluid with the capillary tube.

A puncture in the midline of the abdomen was done on Baby M., a marantic infant, 10 weeks of age. As no fluid was obtained, 15 c.c. of Ringer's solution was injected through the needle which was left in situ. The child was turned in various positions to produce an even distribution of fluid, and after an interval of five minutes, the capillary tube was inserted and fluid obtained. The baby was again turned in various positions, a second interval of five minutes elapsed and fluid was again obtained. The child was then given an intraperitoneal injection of Ringer's solution.

A similar procedure was adopted in the case of Baby P., an ill nourished infant, 3 months of age. However, this child received only 5 c.c. of Ringer's solution. Nevertheless, five minutes after the injection, fluid was obtained with the capillary tube.

In these two cases fluid was withdrawn at the same site at which it was injected. It is conceivable that the omentum or loops of intestine might temporarily have walled off the injected fluid; thus the small effusion characterized by the even distribution of the fluid over the entire peritoneal cavity, was not faithfully reduplicated. The procedure was therefore modified. In the next case, Baby H. R., an ill-nourished infant, 10 weeks old, an abdominal puncture was done in the left lower quadrant, 4½ cm. from the midline. No fluid was obtained, and 5 c.c. of Ringer's solution was injected through the needle which was then withdrawn. Seven minutes later, the abdomen was tapped just below the umbilicus and fluid was obtained. The intraperitoneal injection of Ringer's solution was then completed. This indicates that there is a thorough distribution of small quantities of fluid throughout the

---

4. The cases of peritonitis will be the subject of a later communication and the incidence of free fluid in marasmus is under investigation.

peritoneal cavity, and that extremely small amounts may be demonstrated by the capillary tube.

The rate of absorption of fluid injected into the peritoneal cavity was studied in two series of cases. In the first series, single taps were done a number of hours after one or a series of intraperitoneal injections. Seven cases showed a dry tap from twelve to twenty-four hours after injection. In one case fluid was present twenty hours, and in two cases, twenty-four hours after injection (Table 3).

The second series comprised ten cases. After a preliminary dry tap, fluid was injected and abdominal punctures were performed at stated intervals thereafter. Absorption was variable—from twelve to forty-eight hours. Solutions of different composition were tried. In the first six cases, physiologic sodium chlorid solution or Ringer's solution was used. As injections into the serous cavities of animals

TABLE 3.—Results of Single Abdominal Taps Following Intraperitoneal Injection of Fluid

Name	Age	Weight Lbs.	Oz.	Diagnosis	Hours After Intraperitoneal Injection	Result of Tap	Remarks
D. D.	10 wks.	6	11	Intoxication	12	0	
Wm. N.	4 mos.	9	6	Intoxication	24	0	
Thos. B.	3 mos.	6	..	Intoxication	18	0	
Ed. D.	10 wks.	6	10	Intoxication	24	0	
V. H.	10 mos.	13	8	Intoxication	12	0	
M. C.	8 mos.	15	6	Intoxication	20	0	
M. S.	3 mos.	8	..	Intoxication	24	0	
J. H.	3 mos.	6	6	Intoxication	24	+	16,000 cells per c.mm., culture negative
J. S.	6 mos.	12	4	Intoxication	20	+	15,000 cells per c.mm., culture negative
J. C.	8 mos.	19	2	Intoxication	24	+	12,600 cells per c.mm., culture negative

indicates a more rapid absorption of hypotonic solutions than of normal or hypertonic solutions,[5] a 0.3 per cent. sodium chlorid solution was used in four cases. In this small series, the rate of absorption of the hypotonic solution was not materially more rapid than that of other solutions. Clinical signs of a reaction, such as distention and slight rise in temperature, were identical with those following the injection of physiologic sodium chlorid solution. Although evidence of the distinct superiority of hypotonic solutions is lacking, in our brief experience there is no indication that such solutions are less safe than physiologic sodium chlorid solution (Table 4).

The reaction of the peritoneum was studied by tracing the total and differential cell count (Table 5; Fig. 2). The number of cells

5. Leathes, J. B., and Starling, E. H.: J. Physiol. **13**:106, 1895. Starling, E. H., and Tubby, A. H.: J. Physiol. **16**:140, 1894. LePlay, A., and May, E. S.: Compt. rend. Soc. de biol., Paris, T. 11, 221, 344. Adler, I., and Meltzer, S. J.: J. Exper. Med. **1**:482, 1896.

Name	Age	Weight		Diagnosis	Preliminary Tap	Amount Injected, C.c.	Postinjection Taps Hours After Injection						Composition of Fluid Injected
		Lbs.	Oz.				3	6	12	24	36	48	
L. C.	4 mos.	8	1	Syphilis, acute intestinal intoxication	0	150	+	+	+	+	0	..	Commercial tablets, Ringer's; Sodium chlorid....0.7; Potassium chlorid....0.026; Calcium chlorid....0.03
Wm. W.	3 wks.	6	9	Malnutrition	0	150	+	+	+	0	..	..	Commercial tablets, Ringer's; Sodium chlorid....0.7; Potassium chlorid....0.026; Calcium chlorid....0.03
M. C.	5 mos.	7	12	Acute intestinal intoxication	0	150	+	+	+	0	..	..	Prepared from chemically pure materials*; Sodium chlorid, 0.85 per cent.
M. F.	4 mos.	7	4	Acute intestinal intoxication	0	150	+	+	0	..	..	..	Prepared from chemically pure materials*; Sodium chlorid, 0.85 per cent.
J. M.	2½ mos.	5	6	Marasmus	0	65	..	+	+	+	+	0	Prepared from chemically pure materials*; Sodium chlorid....0.9; Calcium chlorid....0.026; Potassium chlorid....0.01
H. B.	2½ mos.	8	4	Malnutrition	0	150	..	+	+	+	+	0	Sodium chlorid....0.7; Calcium chlorid....0.026; Potassium chlorid....0.01
M. L.	4 mos.	9	..	Malnutrition	0	100	..	..	+	0	..	..	Sodium chlorid, 0.3 per cent.
V. K.	4 mos.	4	..	Marasmus	0	100	..	..	+	+	0[1]	..	Sodium chlorid, 0.3 per cent.
J. T.	7 mos.	10	..	Acute intestinal intoxication	0	150	..	..	+	+[2]	..	..	Sodium chlorid, 0.3 per cent.
J. R.	4 mos.	11	8	Acute intestinal intoxication	0	100	..	..	+	0[3]	..	..	Sodium chlorid, 0.3 per cent.

* Merck's reagent chemicals.
1. Done 30 hours after injection.
2. Done at necropsy; ½ c.c. fluid obtained.
3. Done 20 hours after injection.

rises rapidly from the third and sixth hours to the thirty-sixth hour.
At the peak of the reaction the count rose in most cases to 12,000 and
in one case to 34,000. Not all fluids could be studied in this way.
Some were too thick and mucoid, others clotted too quickly to permit
dilution and the use of the counting chamber, and occasionally only a
drop or two of fluid was obtained. Cultures done on twelve fluids
were negative.

The differential smears were particularly interesting (Table 5).
In one case, in the fresh preparation, large cells were seen putting out
pseudopodia—true ameboid motion. The stained preparations of a
number of the cases showed large vacuolated mononuclear cells con-
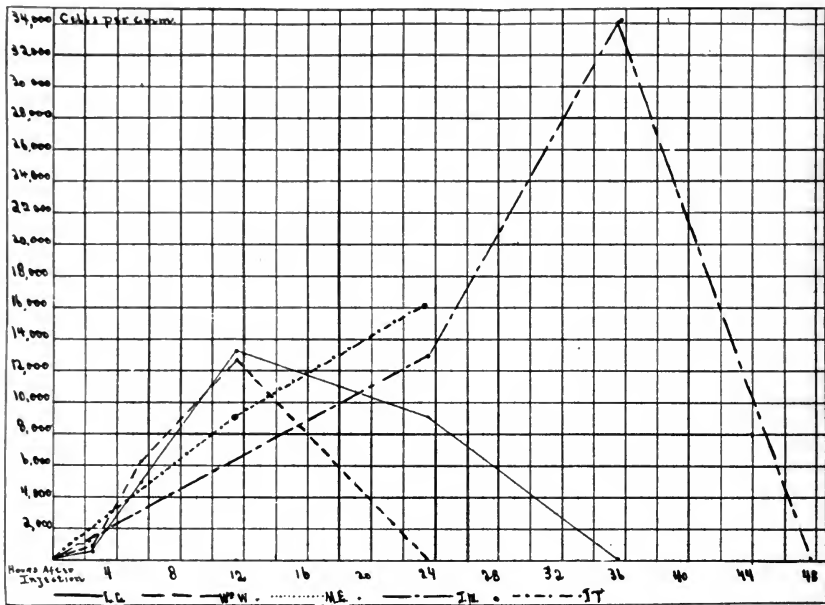
Fig. 2.—Curves showing reaction of peritoneum to injections as determined
by leukocyte count.

taining leukocytes and free chromatin bodies—macrophages or endo-
thelial cells of Metchnikoff. These cells, according to Adami, are
characteristic of the early inflammatory reaction of the peritoneum.[6]
The differential counts do not presume to represent the exact per-
centages of the different cells. The material as mentioned above, was
thick and mucoid and did not lend itself to even distribution on a slide;
also, many of the cells were in various stages of degeneration and
others were distorted by the albuminous matrix and fibrinous strands.
The essential fact is that the peritoneal fluid shows all the character-

---

6. Adami, J. G.: Inflammation, New York, Macmillan & Co., 1907, p. 69.

TABLE 5.—REACTION OF PERITONEUM AS TRACED BY LEUKOCYTE COUNT

Name	Hours After Injection										
	3		6		12		24		36		48
	Total Count	Differential	Total Count	Differential	Total Count	Differential	Total Count	Differential	Total Count	Differential	Differential
L. C.	590	......	4,800	......	13,200	......	9,000	......	......	0	
M. C.	520	......	5,400	......	......	Not done	......	0			
M. E.	700	......	2,800	0	12,800	0	......	0			
Wm. W.	600	Poly. 87 Lym. 13	6,200	Poly. 91½ Lym. 8½	12,800	......	......	0		0	0
J. M.	......	......	......	Poly. 91 Lym. 7 Trans. 2	......	Poly. 84 Lym. 8 Trans. 8	12,900	Poly. 59 Lym. 24 Endo. 13 Trans. 4	34,400	Poly. 68 Lym. 30 Endo. 1 Trans. 1	0
H. R.	......	......	......	Fluid obtained unsatisfactory for total or differential count	......	......	......	Poly. 67 Lym. 29 Endo. ½ Trans. 3½	......	Poly. 60 Lym. 35 Endo. 3 Trans. 2	0
V. K.	......	......	......	......	5,000	Poly. 79 Lym. 20 Trans. 1	......	Poly. 71 Lym. 24 Endo. 1	......	0	
J. T.	......	......	......	......	9,000	Cells degenerated; unsatisfactory	16,000*	Postmortem unsatisfactory			
M. L.	......	......	......	......	......	Poly. 93 Lym. 7	......	0†			
J. R.	......	......	......	......	Quantity insufficient	Poly. 79 Lym. 18 Endo. 1 Trans. 1	......	0†			

Poly. = polynuclear; Endo. = endothelial macrophages; Lym. = lymphocytes; Trans. = transitionals.
* Postmortem.   † Done 20 hours after injection.

istics of an inflammatory reaction—mucoid, sticky, fibrinous fluid, containing endothelial cells and leukocytes—a true chemical peritonitis.[7]

The usual criterion by which one judges whether an intraperitoneal injection may be repeated, is the disappearance of the distention which usually follows injection. We have not kept notes as to the exact hour of the disappearance of this sign. However, in no case did distention persist for as long a period as fluid was demonstrable. The occurrence of a temporary inflammatory reaction and the persistence of a small residue of the previously injected fluid should not contraindicate the repetition of an injection.

SUMMARY

1. Absorption of fluid injected into the peritoneal cavity occurs in from twelve to forty-eight hours.

2. Intraperitoneal injection of saline solutions causes a temporary reaction—a sterile inflammation.

3. Abdominal puncture with a capillary tube provides a safe method for the diagnosis of very small quantities of peritoneal fluid and of following the course of an inflammatory reaction in the peritoneal cavity.

---

7. In the early part of the work, this albuminous fluid rendered preparations stained by the usual methods very unsatisfactory. We wish to thank Dr. B. S. Kline for suggesting a method that produces excellent pictures. The technic is: Fixation in cold 10 per cent. liquor formaldehyd for ten minutes; washing in tap water and staining with aqueous or saturated alcoholic solution of methylene blue.

THE PHYSICAL DEVELOPMENT OF
TUBERCULOUS CHILDREN *

M. L. BLATT, M.D.

Assistant Professor of Pediatrics, University of Illinois College of Medicine;
Attending Pediatrician, Cook County Hospital

CHICAGO

Deficiency in body weight is generally recognized as one of the important early symptoms of tuberculosis. In adults this is frequently synchronous with the appearance of focal symptoms. In childhood, focal symptoms play so unimportant a rôle in the early differential diagnosis of tuberculosis, and are so lacking in pathognomonic features, that it seems necessary to determine whether deficiency in weight can be considered of value.

Two groups of children form the basis of this study: the first group, those of nontuberculous parentage, who were themselves either without any symptoms suggestive of tuberculosis, or who had symptoms and were negative to tuberculin tests. This constituted the control group (614 children). This series was observed in the pediatric department of the West Side Jewish Aid Dispensary. The second group, comprising 508 patients, was observed in the course of a number of years at the West Side Jewish Aid Branch of the Municipal Tuberculosis Sanitarium. These children came under observation as the children of tuberculous parentage, as children suspected of tuberculosis because of poor physical condition, or referred to the tuberculosis department from the pediatric dispensary after a positive diagnosis had been made.

No attempt was made to differentiate between the various types and stages of tuberculous infection. Personal observation leads me to believe that tuberculosis in early childhood remains an acute disease over an undetermined number of years, and that there is no method which enables one to determine the activity or quiescence of the infection. The diagnosis of the tuberculosis was based on physical findings and the von Pirquet test. The physical findings were very largely those of bronchial and hilus gland involvement. This group of children, under observation for several years, was studied to see if a conclusion could be drawn as to the effect of a recognized tuberculous infection on the height and weight.

The majority of cases were tested with both bovine and human tuberculin. No case was recorded as positive unless it gave the characteristic reaction to tuberculin. This point is mentioned because it is

---

my opinion that physical findings are not sufficient grounds for the diagnosis of tuberculosis in the absence of the positive tuberculin reaction (except when overwhelming infections with the tubercle bacillus are present, or the acute exanthemata, especially measles and scarlatina. It is also likely to be negative in pertussis and pneumonia). The basic clinical work of von Pirquet, the observations of Franz Hamburger, and the combined clinical and pathological study made by Gohn, prove conclusively that the infection may be demonstrated postmortem in cases in which the cutaneous test was positive during life.

In order to establish a foundation of normal height and weight of children in this district, a control group was used. The comparison of this group with the ideal weights given by the Children's Bureau of the Department of Labor, shows clearly the necessity for comparing special groups of children with like groups from the same social status, living in a similar environment. Only by such comparison is it possible to minimize errors in deduction.

I will first consider the statistics (Tables 1 to 6) which have to do with the initial height and weight of the boys and girls in the three groups, namely, Children's Bureau, Control and Tuberculous. From these tables, charts were plotted indicating graphically the measurements at half year periods, from 1 to 14 years, inclusive.

The tuberculous and control curves do not rise evenly like those of the Children's Bureau. The reason for this is that there was not the same number of observations in each age period, and the total number in each series was relatively small (tuberculous 508, control 614) in comparison with the thousands of children observed by the Children's Bureau.

It also appears more than a coincidence that the depressions and elevations of the tuberculous and control curves should so closely correspond as they do. The explanation seems to be that the children of these series came from a small district in which hygienic, dietetic, economic, and social conditions were decidedly adverse, so that while there is a well marked difference in their heights and weights, nevertheless their measurements rose and fell in rather parallel fashion.

The features that have been especially noted are: (1) The number of points at which the control and tuberculous lines have risen above the Bureau line, indicating the number of age groups that have been normal in the available statistics; (2) the number of individuals represented by these normal age groups, and (3) the percentage of the series that came up to the Bureau standard.

These three observations are represented in a column, indicative of the percentage of normality of the control and tuberculous groups in comparison with the Children's Bureau standard, represented as 100 per cent.

TABLE 1.—HEIGHT AND WEIGHT OF TUBERCULOUS BOYS (256)

Age. Years	Number of	Initial Measurements		Period of Observation in	Average Gain in This Period		Average Gain per Year While Observed	
		Height, Inches	Weight, Pounds		Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	1	....	20.2	35.0	....	15.8	....	5.4
1½	2	....	22.4	25.0	....	9.5	....	4.5
2	6	33.1	24.6	30 8	7.5	10.2	2.3	3.9
2½	6	35.7	28.7	27.6	7.4	9.9	3.2	4.3
3	4	37.0	31.6	50.0	10.2	20.4	2.4	4.8
3½	1	....	34.7	51.0	....	16.5	....	3.8
4	12	38.2	34.5	29.6	7.0	10.3	3.0	4.1
4½	2	40.3	31.5	14.0	1.7	3 0	1.4	2.5
5	15	41.0	38.4	35.3	6.8	14.6	2.2	4.9
5½	7	43.0	39.1	36.0	4.8	9.8	1.6	3.2
6	11	44.8	41.6	35.1	5.6	14 0	1.9	4.7
6½	2	....	43.3	51.5	....	21.2	....	4 9
7	30	46.1	45.9	34.3	5.5	16.5	1.9	5.8
7½	8	45.9	47.9	25.7	4 3	12.8	2.0	5.9
8	29	48.1	52.9	31.7	3.5	19.2	1.3	7.2
8½	2	45.0	50.7	15.0	....	24.5	....	19.6
9	24	49.2	57.2	24.5	4.6	13 0	2.2	6.3
9½	3	41.6	56.6	21.3	10.1	12 5	5.6	7.0
10	28	52.2	58.1	28.0	4.6	20.9	1.9	8.9
10½	1	....	67.5	29.0	....	23.5	....	9.7
11	12	51.9	61.1	17.9	4.3	12.2	2.8	8.1
11½	..	....	....	....	....	....	....	....
12	17	54.0	68.7	17.0	4.2	20.5	2.9	14.4
12½	7	53.8	73.3	14.0	6.3	12.3	5.3	10.5
13	13	55.1	75.6	19.7	4.1	14.2	2.4	8.6
13½	3	58.1	92.5	25.0	8.0	27.9	3.8	13.3
14	10	56.7	82.2	22.5	5.2	14.3	2.7	7.6

TABLE 2.—HEIGHT AND WEIGHT OF TUBERCULOUS GIRLS (252)

Age. Years	Number of	Initial Measurements		Period of Observation in	Average Gain in This Period		Average Gain per Year While Observed	
		Height, Inches	Weight, Pounds		Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	2	....	22.9	33.0	1.0	12.3	0.3	4.4
1½	2	....	20.5	16.0	....	5.0	....	3.7
2	6	39.1	24 4	23.0	3.8	8.1	1.9	4.2
2½	5	35.8	30.6	49.5	10.7	23.9	2.6	5.7
3	9	34.6	29.3	19.4	3.9	6.1	2.4	3.7
3½	1	38.0	32.5	23.0	15.2	6.7	7.9	3.4
4	11	39.5	32.8	33.0	5.7	15.0	2.0	5.4
4½	1	37.0	29.0	29.0	....	9.2	....	3.8
5	13	40.9	36.3	25.9	5.5	11.7	2.5	5.4
5½	2	41.0	35.9	21.0	2.3	8.2	1.3	4.6
6	19	42.9	42.0	27.4	3.8	10.1	1.6	4.4
6½	3	43.7	39.1	44.6	6.9	18.4	1.8	4.9
7	16	44.2	42.9	32.1	6.3	14.7	2.3	5.4
7½	1	....	46.5	69.0	....	51.2	....	8.9
8	19	47.4	49.7	34.9	5.9	19.6	2.0	6.7
8½	8	48.1	48.2	26.7	4.4	20.2	1.9	9.0
9	21	49.0	53.0	21.0	4.9	12.3	2.7	7.0
9½	3	49.8	56.1	27.0	10.2	15.4	4.5	6.8
10	26	50.1	58.2	26.6	5.0	20.3	2.2	9.1
10½	2	53.8	67.7	14.0	3.7	15.0	3.1	12.8
11	41	52.7	62.0	25.7	3.2	15.1	1.4	7.0
11½	..	....	....	....	....	....	....	....
12	14	57.5	68.7	28.0	1.6	20.7	0.6	8.8
12½	3	53.8	72.1	20.5	5.0	35.9	1.9	20.1
13	17	58.0	82.6	18.8	9.8	22.7	6.2	14.4
13½	2	61.7	77.0	18.0	1.5	12.2	1.0	8.1
14	5	52.6	83.1	9.0	0.9	2.5	1.1	3.3

TABLE 3.—HEIGHT AND WEIGHT OF CONTROL BOYS (277)

Age, Years	Number of Cases	Initial Measurements		Gain per Year*	
		Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	9	....	16.3	....	....
1½	25	22.4	23.2	....	3.5
2	13	33.0	30.1	3.1	2.4
2½	4	35.2	28.0	2.2	3.9
3	20	35.4	30.0	2.3	3.6
3½	12	37.0	30.5	2.4	4.4
4	17	36.6	34.0	3.0	3.6
4½	5	41.0	36.4	2.7	2.1
5	20	40.4	37.6	2.3	4.1
5½	7	41.1	37.7	2.3	3.7
6	17	42.6	41.1	2.3	4.5
6½	4	42.2	42.0	1.9	6.4
7	19	45.0	44.0	1.5	4.8
7½	1	48.0	49.5	0.7	2.4
8	19	47.0	49.7	2.4	9.1
8½	4	48.0	49.0	0.8	4.5
9	16	49.5	54.5	1.3	4.4
9½	4	48.5	54.7	....	7.3
10	11	49.4	54.7	2.5	9.8
10½	4	53.5	74.0	1.9	1.4
11	12	52.6	63.6	0.9	....
11½	1	53.0	72.0	....	....
12	6	55.8	80.8	2.2	9.6
12½	..	....	....	2.2	....
13	20	57.0	77.6	....	....
13½	1	59.0	94.5	....	....
14	6	58.5	88.3	....	....

* This figure was computed by dividing the average gain, for a period equal in length to that of the tuberculous groups, by 12.

TABLE 4.—HEIGHT AND WEIGHT OF CONTROL GIRLS (337)

Age, Years	Number of Cases	Initial Measurements		Gain per Year*	
		Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	28	....	17.4	....	5.8
1½	13	....	29.0	....	0.0
2	12	32.8	25.5	1.9	4.1
2½	6	36.0	27.6	2.0	4.1
3	19	33.4	28.4	3.6	5.6
3½	12	35.2	29.0	3.1	4 5
4	21	36.6	33.4	2.5	3.0
4½	8	39.3	37.5	1.7	1.9
5	19	44.4	36.6	....	3.4
5½	8	42.0	37.7	0.9	3.5
6	21	42.3	39.4	1.5	3.8
6½	7	44.5	44.6	1.5	4.9
7	19	43.5	42.3	1.8	4.9
7½	8	44.0	47.2	1.7	3.8
8	20	45.5	47.7	2.4	5.6
8½	9	46.3	49.0	2.5	5.3
9	22	48.5	53.5	1.5	4.1
9½	..	....	....	....	....
10	29	50.0	63.0	2.7	3.1
10½	7	51.2	59.4	4.0	9.4
11	11	52.6	63.2	0.6	1.3
11½	1	56.0	70.5	....	....
12	16	....	....	....	....
12½	1	56.0	69.7	0.3	11.5
13	13	54.0	66.0	1.2	5.7
13½	1	54.0	62.7	....	....
14	6	56.6	89.4	....	....

* This figure was computed by dividing the average gain, for a period equal in length to that of the tuberculous groups, by 12.

TABLE 5.—WEIGHT AND HEIGHT OF BUREAU OF CHILDREN—BOYS

Age, Years	Measurements		Gain per Year (As in Table 3)	
	Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	29.3	21.8	3.3	4.7
1½	31.7	24.6	3.3	4.3
2	33.7	27.1	2.6	4.4
2½	35.3	29.5	2.4	4.4
3	37.1	32.2	2.0	4.0
3½	38.6	33.7	2.0	4.4
4	39.5	35.8	2.1	4.5
4½	40.5	38.4	2.1	4.6
5	41.6	41.1	2.1	4.3
5½	42.7	43.1	2.0	4.4
6	43.8	45.2	2.0	4.7
6½	44.7	47.1	2.0	5.6
7	45.7	49.1	1.9	5.3
7½	46.7	51.5	2.0	5.4
8	47.8	53.9	1.8	5.5
8½	48.7	56.5	2.0	5.7
9	49.7	59.2	1.7	5.3
9½	50.7	62.2	1.6	5.4
10	51.7	65.3	1.7	6.0
10½	52.3	67.7	1.9	7.0
11	53.3	70.2	1.8	7.0
11½	54.2	73.5	...	...
12	55.1	76.9	2.3	9.1
12½	56.1	80.8	2.3	9.1
13	57.2	84.8	2.6	11.1
13½	58.5	89.8	2.5	12.0
14	59.9	84.9	2.8	12.4

TABLE 6.—WEIGHT AND HEIGHT OF BUREAU OF CHILDREN—GIRLS

Age, Years	Measurements		Gain per Year (As in Table 3)	
	Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	28.8	20.7	3.3	3.8
1½	31.1	23.3	3.6	5.0
2	33.3	26.3	2.8	3.7
2½	34.8	28.2	2.3	4.1
3	36.7	30.5	2.1	3.8
3½	38.0	32.5	2.2	4.6
4	39.0	33.7	2.1	4.6
4½	40.1	36.7	2.2	4.4
5	41.3	39.7	2.1	5.7
5½	42.3	41.5	2.1	3.6
6	43.4	43.3	2.0	3.0
6½	44.4	45.4	2.0	5.6
7	45.5	47.5	1.9	4.8
7½	46.5	49.7	2.1	7.1
8	47.6	52.0	1.8	6.1
8½	48.5	54.5	1.9	6.2
9	49.4	57.1	1.9	5.7
9½	50.3	59.7	2.1	7.1
10	51.3	62.4	1.9	7.3
10½	52.3	65.6	2.3	8.2
11	53.4	68.8	2.3	10.0
11½	54.6	73.5	...	....
12	55.9	78.3	1.8	10.7
12½	57.0	83.5	1.8	9.4
13	58.2	88.7	1.4	8.6
13½	59.0	93.5	1.4	8.3
14	59.9	98.4	1.2	7.5

A study of the heights of boys shows that whereas seven of twenty-one tuberculous groups were normal in comparison with the Children's Bureau standard, the boys of the control series were normal in only five of twenty-five age periods. Furthermore, the number of individuals in these normal groups was 112 of 256 for tuberculous boys, or 43.75 per cent., but only 17 of 277 for control boys, or 6.13 per cent. In other words, the tuberculous males reached or surpassed the Bureau requirements for height seven times as often as those of the control series.

The figures for the girls of the tuberculous and control groups are less striking. The tuberculous girls were normal in six of twenty-three age periods while the control girls equalled the standard in only four of twenty-three age groups. The percentage of normality for these groups was 13.88 (35 of 252) for the tuberculous girls and 9.79 (33 of 337) for the controls. We note a definite though less marked superiority of the tuberculous females.

The tuberculous boys were normal in only two of twenty-six age periods, while the males of the control series were up to par in four of twenty-six groups. There were only four of 256, or 1.56 per cent., tuberculous boys who were of normal weight. However, twenty-four of 277 (8.66 per cent.) control boys reached the Bureau standard, almost five and one-half times as often as the members of the tuberculous series.

A consideration of these results shows that the type of boy in the tuberculous group was one whose height more frequently reached that of the Children's Bureau standard than did the control boy, but whose weight far less often was normal.

As for the weights of girls, it is apparent that three of twenty-six tuberculous groups were normal, while in the control group three of twenty-five were normal. With reference to the individual cases it is shown that 14.83 per cent. (50 of 337) of the control girls attained the Bureau standard, but only 1.98 per cent. (5 of 252) of the tuberculous series attained that standard. The control girls were thus strikingly more often of normal weight than the tuberculous girls (7 : 1).

Here, as with the boys, the tuberculous girl is comparatively taller but of a lesser weight than her sister of the control series. Both are much below the Children's Bureau standard.

With reference to height, the tuberculous boys were normal in 150 of 256 cases, or 58.59 per cent., as compared with 43.75 per cent. (112 or 256) of the averages for age groups. The control males were equal to the bureau norm in 88 or 243 observations, or 36.21 per cent., a figure which is much higher than the 6.13 per cent. (17 of 277) for height.
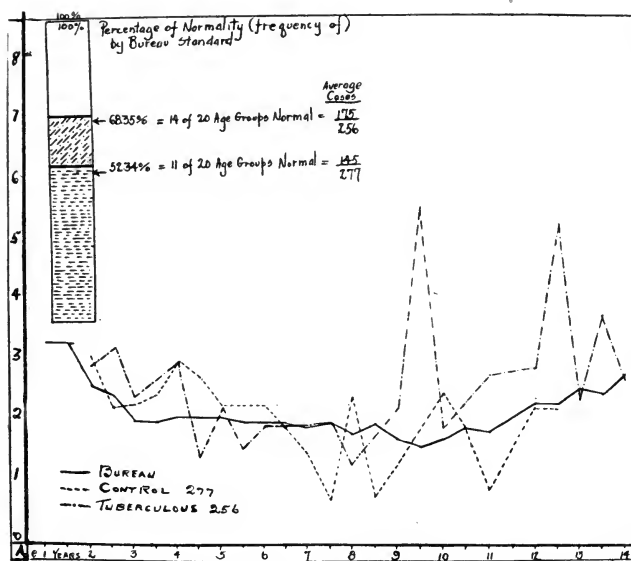
Fig. 1.—Average gain in inches of different groups of boys per year.
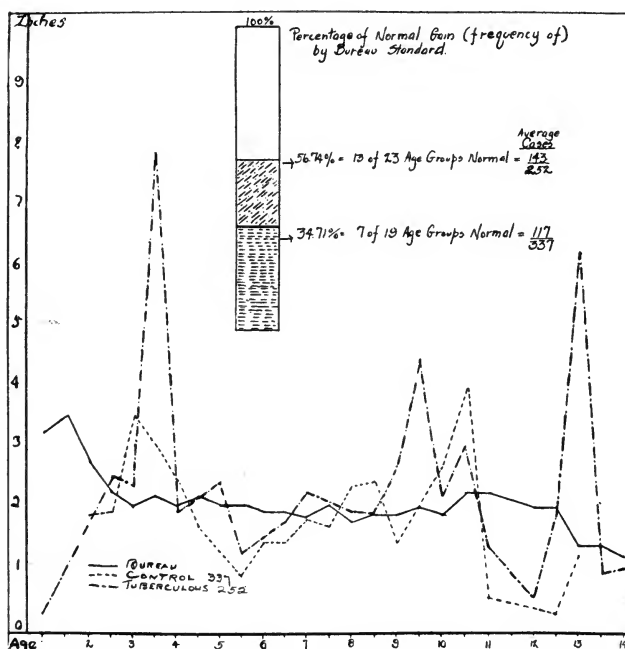
Fig. 2.—Average gain in inches of different groups of girls per year.

The weight of the tuberculous boys reached the standard in 11.32 per cent. (29 of 256) as compared with the 1.56 per cent. (4 of 256) of the averages for age groups. Similarly, the percentage of normality is higher for control boys, 25.52 per cent. (74 of 277).

However, the fact remains that the tuberculous boys were more often of normal height than the controls, but were not as frequently of the normal weight.

As for the height and weight of girls, the tuberculous girls were of normal height in 58.29 per cent. (147 of 252) in contrast to 33.22 per cent. (98 of 295) for the controls.

With reference to weight, however the tuberculous girls were normal in only 1.98 per cent., and the controls in 14.83 per cent. Our individual observations, instead of average, indicate that the tuberculous girls were normal in 26.19 per cent. of the cases (66 of 252) while the control girls were slightly below this percentage, 23.69 per cent. (80 of 336 observations). The explanation for the difference lies in the fact that a large number of the individuals in the subnormal average age groups were equal to the Bureau norm.

The heights and weights of the boys and girls were added to give a composite. The tuberculous children were up to the standard in height in 58.47 per cent. of the cases (297 of 508), and the controls in 35.58 per cent. (186 of 538), so that the tuberculous child in individual instances attained the Children's Bureau norm, 22.89 per cent. (58.47— 35.58), more frequently than the control.

However, the tuberculous child was less often of normal weight, 18.71 per cent. normality (95 of 508), as contrasted with 25.05 per cent. (154 of 615) for the control individual.

My conclusion as to tuberculosis in childhood is that given a group of children below the norm in height and weight, the tuberculous child will more frequently appear to be of normal height, but far less often of normal weight. The tuberculous individual is often seen as the lanky child.

This concludes the observations on the initial heights and weights of the groups.

Tables 1 and 2 show the average length of time of observation in months for the various age groups. The minimum average period for boys was 14 months, and the maximum 51.5 months: for girls the minimum was nine months, and the maximum 69 months. The curves for control and Bureau were secured by calculating what these groups would have gained per year had they been watched for a period equal to that over which the tuberculous children were observed. For example: The height of a Bureau boy of three years is 37.1 inches. If this child had been observed for 50 months, as was the tuberculous boy of the
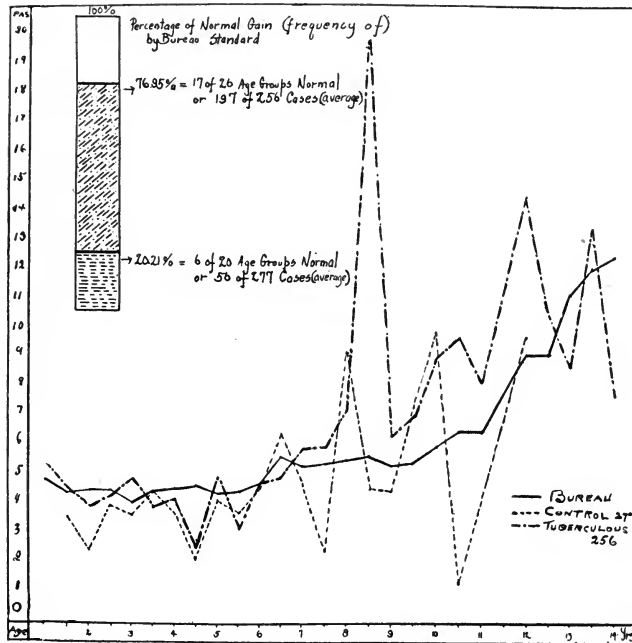
Fig. 3.—Average gain in pounds of different groups of boys per year.
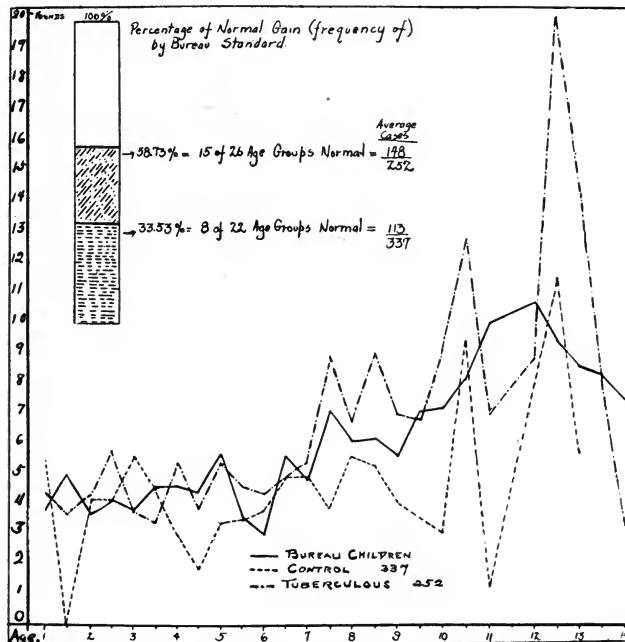
Fig. 4.—Average gain in pounds of different groups of girls per year.

corresponding group, his height would have been 45.7 inches, a gain of 8.6 inches in this period of 4 2/12 years. His gain for a year would have been 12/50 of 8.6 inches, or 2.0 plus inches. In Chart 1 this figure was plotted. Similarly the gain was secured for other periods of the Bureau and the control series and plotted. With the Bureau curve as the standard the relative average gains of the tuberculous and control groups were studied. The tuberculous curve stands well above the control and the Bureau lines. The essential point to me appears to be how many of the tuberculous and control groups attained the Bureau norm.

Chart 1 shows the average gain in inches per year of boys in the three series. In fourteen of twenty age periods, the tuberculous boys crosses the curve of the Bureau standard, while eleven of twenty of the controls did likewise. These groups represent 175 of 256 tuberculous males, or 68.35 per cent. gained as well or better than the Bureau standard; while a smaller number, 145 of 277 control boys, representing 52.34 per cent. reached or passed the norm. Thus it is apparent that the tuberculous boys attained the standard more often than the control boys.

Chart 2 indicates the comparative average gain per year in height of the girls of the three series. In thirteen of twenty-three age periods the tuberculous girls attained the norm (56.00 per cent.) while in seven of nineteen (37.00 per cent.) the control females were up to par. More than half of the tuberculous girls equalled or surpassed the Bureau standard, 143 of 252 or 56.74 per cent. In contrast, the control girls were normal in height gain in 34.71 per cent., 117 of 337 cases.

Thus the tuberculous girls, even as the boys, equalled the Bureau gain more frequently than the control. It is interesting to note that in the very much undernourished control and tuberculous series the boys gained uniformly more normally than the corresponding girls. This fact is in accordance with the common observation in normal children, that on the whole boys gain better and are taller than girls.

Chart 3 demonstrates the remarkable better gain of the tuberculous boys over the control series. In 76.95 per cent. of the cases (197 of 256) and in seventeen of twenty-six age groups the tuberculous males attained the standard weight gain. The control males were up to par in only six of twenty age groups, 20.21 per cent. for 50 of 277 cases. As for degree of pound gain, the tuberculous line rises markedly after the age of seven.

The tuberculous girls (Chart 4) did not as frequently attain the Bureau weight gain as did their brothers. In fifteen of twenty-six age groups there were 148 normals of 252 (58.73 per cent.) while the controls crossed the norm in eight of twenty-two age groups for a total of 113 of 337 observations, or 33.53 per cent. The tuberculous girl

gained in weight normally in 25.20 per cent. more instances. Here likewise the degree of weight gain is very marked from the age of seven on, in the tuberculous series.

The superiority in gain in height and weight per year of the tuberculous series has been plotted in Chart 5. The frequency of normal gain in height per year of the tuberculous child was 62.59 per cent. (318 and 508 observations) as contrasted with 42.67 per cent. (262 of 614 observations) for the control child. In 67.91 per cent. of the cases (345 of 508) the tuberculous child attained the Children's Bureau standard, while the control child did as well in but 27.52 per cent. (169 of 614).
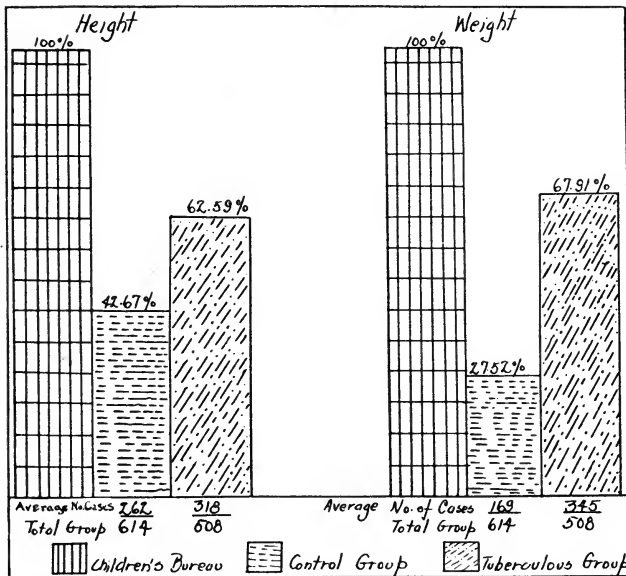
Fig. 5.—Composite of boys and girls. The percentage of normal gain per year of observation in comparison with the children's bureau standard.

CONCLUSIONS

1. Using height and weight as the basis of comparison, tuberculous children more frequently attained the normal standard of gain than those of the control series.

2. Neither the entire tuberculous nor control series reached the Children's Bureau standard, represented as 100 per cent., although the tuberculous group more frequently approached it.

3. The superiority of the tuberculous over the control series in gain, I believe to be dependent on the improvement in sanitation, food, and the removal of defects.

4. *The child with hilous or tracheobronchial gland tuberculosis in a group of children under-height and under-weight, when properly treated, will more often be the one to attain the normal gain.* This observation, according to my experience, is equally applicable to cases seen in private practice.

PROGRESS IN PEDIATRICS

RÉSUMÉ ON THE CIRCULATORY SYSTEM LITERATURE OF 1920 *

HENRIETTA CALHOUN, M.D.
State University of Iowa
IOWA CITY

THE HEART

The *electrocardiogram* during the past year has become more extensively used, and more carefully studied. There are many points on which observers disagree, but certain fixed conclusions stand out clearly and its value in aiding diagnosis is undisputed. It is interesting to learn that in all of Paris Ribierre [1] knows of only two hospitals equipped for electrocardiography. To remedy this he suggests that medical societies in the smaller cities should acquire equipment to be loaned to the members.

Mann [2] describes his monocardiogram, which is an attempt to combine the graphs obtained in Leads I, II and III into a single curve. It is based on the fact that Lead II equals Lead III plus Lead I or the algebraic sum of the ordinates in Leads III and I at the same instant. By finding the location of the center of negativity at subsequent time intervals and connecting these points a curve is formed representing the cardiac cycle. This monocardiogram is a fusion of the three leads into a single curve by an algebraic reversal of the process by which the leads are obtained.

Hamburger [3] studies the changes in the P wave, which represents *the auricular complex*. The physiologic P complex is an upright wave which results from auricular systole. It expresses the origin of the heart beat at the normal site of the impulse formation, and the passage of the wave through the auricular tissue in definite directions. Alterations in the height, direction and configuration are caused by abnormal auricular conditions. Twenty per cent. of the 300 electrocardiograph curves at the Michael Reese Hospital (Chicago) show an inverted P wave, usually in Lead III. The P wave may be inverted by vagus stimulation, by the impulse originating in the lower portion of the auricle, by force expiration, and by digitalis. The P wave may be

* Received for publication, Jan. 25, 1921.
1. Ribierre, P.: Méd. mod. **1**:325 (March) 1920.
2. Mann, H.: Arch. Int. Med. **25**:283 (March) 1920.
3. Hamburger, W. W.: Arch. Int. Med. **26**:232 (Aug.) 1920.

persistently inverted, or an inverted P wave may sometimes become upright with atropin. In *auricular paroxysmal tachycardia* the P wave is apt to be inverted. White [4] analyzes a series of electrocardiograms in which the P wave is normal and the origin of the beat is not ectopic or, at least, if it be ectopic, it originates close to the normal pacemaker in the sinoauricular node. This is Galli's nomotopic (nomos = custom, topos = place) type of paroxymal tachycardia, and it has a better prognosis than the usual paroxysmal tachycardia. When the pacemaker moves toward the ventricle there is a tendency toward shortening the P-R interval unless there is a simultaneous vagal stimulation, and the P wave is flattened and finally inverted. White includes in the series two electrocardiograms of sino-auricular heart block not due to digitalis. There are few electrocardiograms of similar conditions in the published records.

Lewis [5] and others, in a series of papers on *flutter and fibrillation*, have brought out a new conception of the arrangement of the muscles in the auricle, and of the path of the excitation wave through these muscles. Auricular flutter shows in the electrocardiogram rapid, contiguous waves uniform in extent and outline. The excitation wave passes through the auricle in a regular sequence from cycle to cycle, without any moment when all the muscle fibers are at rest, as they are in true diastole. The rates of conduction are slower than the rate with normal rhythm, and the direction of the wave of excitation after flutter is established has no relation to the point at which stimulation is applied. When the course is distinctly displayed it extends around the mouths of both the superior and inferior vena cava veins, probably in "a continuous circus movement in a natural ring of muscles existing in the intact heart." It may run either clockwise or counterclockwise. The auricular appendages and the sleeves of muscle on the great veins are supplied by excitation waves centrifugally from the body of the auricle—waves thrown off from the central path as the central wave revolves, so that the direction of the wave in these outlying paths is constant, and depends on the direction of movement in the central path. The basis of flutter is a "circus movement following a central path in the auricles." After long continued experimental flutter in dogs, there are slight variations in the path which Lewis classes as impure flutter. Experimentally, the processes of auricular flutter, impure flutter and auricular fibrillation are linked as parts of a whole complex.

4. White, P. D.: Arch. Int. Med. **25**:420 (April) 1920.
5. Lewis, Th.: Heart **7**:127, 131, 247, 293 (April, Aug.) 1920.

Eyster and Meek [6] have a casette changing mechanism allowing two roentgenograms of the human heart to be taken in the same cardiac cycle. With a simultaneously recording electrocardiograph, they get curves from which the exact incidence of the exposures in the cardiac cycle may be determined. No single border of the heart may be used as an accurate index of contraction, the movement of the entire outline must be considered. The associated electrocardiograms and the roentgenograms show that most of the filling of the ventricle occurs shortly after the ventricle relaxes, and it is almost completed before the auricle contracts. The auricular rôle in adding blood to the ventricles is slight.

Bazett [7] finds that the duration of the *ventricular complex* in the electrocardiogram of the normal heart is a function of the pulse rate and may be determined by the formula Systole $= \sqrt{}$ cycle where $K = 0.37$ for males, and 0.40 for females. Exercise causes an increase in K, and an augmented vagal inhibition lowers K. Wiggers and Katz,[8] determining the cycle length and the duration of systole in a slow vagal heart beat, construct a probable volume curve for each animal and devise a plot of the theoretic relation between the length of systole and the cycle of any heart rate where the heart beats according to a uniform law. The accelerator nerves act on the ventricular muscles causing a reduction of the contraction period.

Brugsch and Blumenfeld [9] record heart sounds on phonocardiograms, controlled by electrocardiograms made at the same time in order to study the proportionate duration of ventricular systole expressed as a per cent. of the complete cardiac cycle. The variation in the different individuals and in the sexes is slight. The percentage length of ventricular systole increases with age. From 25 to 70 years of age the value is from 33.5 to 37.5 per cent. In aortic and mitral insufficiency the proportional duration of systole increases with the severity of the disease.

Fahr [10] follows the *wave of excitation through the ventricles* by following the change in direction of the vector or potential difference through a heart cycle, and then applying what we know of the structure of the His-Tawara-Purkinje system; of the rates of conduction through ordinary muscle; and of the time of onset of the first heart sound and the ventricle pressure wave. The method of the equilateral triangle is accurate within $\pm$ 10 degrees, and is used for determining the frontal plane projection of the direction of potential difference in the human

6. Eyster, J. E. A., and Meek, W. J.: Am. J. Roentgenol. **7**:471 (Oct.) 1920.
7. Bazett, H. C.: Heart **7**:353 (Aug.) 1920.
8. Wiggers, C. J., and Katz, L. N.: Am. J. Physiol. **53**:49 (Aug.) 1920.
9. Brugsch and Blumenfeld: Berl. klin. Wchnschr. **56**: (Oct. 6) 1920.
10. Fahr, G.: Arch. Int. Med. **25**:146 (Feb.) 1920.

ventricle, and the manifest value. The ventricular wave of excitation begins in the subendocardial layer of the Purkinje network, developing a little earlier in the right ventricle, then spreads to the apical layers causing the Q wave. The excitation process extends to the basal arborizations of the Purkinje network, giving the anacrotic limb of R. In the meantime, the process has spread from the apical network to the apical heart muscle, and when the peak of the R wave is reached, the negativity of the apical muscle fibers is great enough to neutralize the preponderance of basal Purkinje arborizations and to cause the catacrotic limb of R and the S peak. At the base of the heart, the excitation process is extending from the basal Purkinje network to the muscles, and their negativity increases until the effect of the apical fibers is reduced and the S wave is reduced. The negative process at the apex dies first, leaving a negative preponderance at the base, causing the T wave. In hearts with left sided enlargement, the electrocardiograph changes are due to an increase in the length of the conducting path in the right ventricle, the right side receiving its negativity first while in right sided enlargement the preponderance of negativity is on the left side. In otherwise normal hearts the form of the Q R S group is dependent on the relative weights of the two ventricles. The interpretation of the ventricular complex is not always clear. Pardee [11] says that hypertrophy of the left ventricle is expected to show a tall R wave in Lead I, with an absent S; and a small or absent R with a deep S wave in Lead III. Hypertrophy of the right ventricle is expected to show a relatively small R with a deep S Lead I and an absent S and a tall R wave in Lead III. The simplest most accurate formula for the L/R ratio is that of Lewis $(R_1 + S_3) - (S_1 + R_3)$. An increased L/R ratio gives R_3 relatively small and R_1 and S_1 large. This is a left predominance. A decreased L/R gives R_1 small and S_1 and R_3 relatively large.

Willius [12] studies changes in the form of the *initial ventricular complex* which is represented by the Q R S waves of the electrocardiogram. Willius divides a series of 747 cases into two groups—Group 1, including 14 per cent., shows a notched Q R S complex, while Group 2 shows slurred or thickened Q R S. In the first group more than half of the cases had predominance of the left ventricle, and the etiologic factors in order of their frequency are: (1) degenerative processes; (2) infections; (3) local nutritional disturbances, and (4) congenital heart disease. In the second group, the etiologic factors are infection and degeneration. Notched and thickened Q R S complex is frequently found in undoubted cases of myocarditis and probably means local disorders in the ventricular myocardium. Smith [13] gives

11. Pardee, H. E. B.: Arch. Int. Med. **25**:683 (May) 1920.
12. Willius, F. A.: Arch. Int. Med. **25**:550 (May) 1920.
13. Smith, F. M.: Arch. Int. Med. **26**:205 (Aug.) 1920.

a good review of the literature on atypical Q R S waves, and in experimental study in dogs of variations in the Q R S waves to determine the effect of lesions in the main branches of the A-V bundle, and of the arborizations of the bundle. His most interesting finding is that arborization block does not explain abnormal Q R S waves. Fatigue alone does not explain abnormal Q R S waves.

Fahr [10] explains that the *diagnosis of right and left bundle branch* lesion is probably made wrong, that in left bundle branch lesions R should be high in Lead I and S deep in Lead III and in right bundle branch lesion S should be deep in Lead I and R high in Lead III. Wilson and Herrmann [14] disagree with this view of Fahr concerning a mistake in the interpretation of the meaning of right and left bundle lesions. They say that in man the excitation wave passes down the Purkinje network of the septum, then upward through the network of the free walls inactivating the muscle in the same order. A lengthened P-R interval means delayed conduction through the A-V node or the main stem of the bundle of His. A lengthened Q R S depends on the thickness of the septum and is the most reliable sign of bundle branch block, the increase in amplitude having less value. The notching of Q R S complex is not uncommon in a normal electrocardiogram. The diagnosis of arborization block is on very shaky ground. The cause of the exaggerated T is not well understood. T deflection is produced by deactivation of the ventricular bundle.

Pardee [15] gives the electrocardiogram of a woman believed to have a lesion in the left ventricle, due to *occlusion of a coronary artery,* who died of an attack of angina pectoris two years later. A day or two after the obstruction the electrocardiogram shows the Q R S group usually notched in two leads, with prominence of the left ventricle. The T wave does not start from the zero level in Leads I and III. It quickly turns away, from the starting point in a sharp curve, without the short straight stretch preceding the peak of the T wave which is so evident in normal records. There are five other records in the literature that are similar. Klewitz [16] finds a negative T peak only in cases of organic heart disease, especially with myocardial lesions, but its absence does not rule out heart disease. Herrmann [17] adds electrocardiograph findings in six more cases of coronary thrombosis with ventricular tachycardia, three of which were proven at necropsy to be cases of coronary thrombosis. On of these is the first clinical case recorded which substantiates the experimental work of Lewis.

14. Wilson, F. N., and Herrmann, G. R.: Arch. Int. Med. **26**:153 (Aug.) 1920.
15. Pardee, H. E. P.: Arch. Int. Med. **26**:244 (Aug.) 1920.
16. Klewitz, F.: Deutsch. Arch. f. klin. Med. **129**:41 (April 29) 1919.
17. Herrmann, G. R.: J. Missouri M. A. **17**:406 (Oct.) 1920.

All six patients clinically had severe anginal attacks and pulse rates from 170 to 250 per minute and the electrocardiograms are those of paroxysmal ventricular tachycardia.

Bishop [18] offers two cases showing early signs of *ventricular fibrillation* as periods of ventricular tachycardia which he considers a serious factor in sudden death from heart failure, due either to fatigue of the ventricular muscles from the rapid rate of contraction or to fibrillation of the ventricle.

McCulloch,[19] studying *electrocardiograms from athreptic infants,* finds alterations of the cardiac mechanism in two cases; in the form of a delayed auriculoventricular conduction and changes in the Q R S complex. These alterations disappear as the child improves.

Jones [20] made *electrocardiographs after the cessation of spontaneous respiration* in a case of cerebral hemorrhage where the heart beat for fifteen hours after normal respiration ceased, and intratracheal insufflation was used; after twelve hours under artificial respiration the heart has normal rhythm, with some lengthening of the ventricular complex that may at times exceed 0.5 second in duration.

Klewitz [21] finds that the *electrocardiogram in persons asleep* differs materially from the electrocardiogram of the same person awake. During sleep the heart cycle is lengthened, the ventricular systole is proportionately prolonged. In different forms of heart disease no regularity can be detected in the sleep change, one case of bradycardia showing a shortened heart cycle.

Josue [22] uses *auscultation of the venous pulse* to obtain information otherwise obtainable only by cardiograph methods. With the patient flat, and the head low, the stethoscope is applied between the sternal and clavicular attachments of the sternocleidomastoid muscle. The stethoscope should almost parallel the neck axis, slanting downward, backward and inward, pointing to the mediastinum. It is applied just back of and as close to the clavicle as possible, with a minimal amount of pressure. The sounds resemble the peaks in the electrocardiogram, and may be interpreted by the radial pulse relationship.

VAGUS EXCITABILITY OF THE HEART

Vagus control and the cardiac reflexes have been the subject of numerous experiments. Laslett [23] examined 108 persons in whom there was a striking reaction to vagus pressure, the mechanism being determined by slowing of the venous or radial curves. There is little

18. Bishop, L. F.: Ann. Med. **1**:58 (April) 1920.
19. McCulloch, H.: Am. J. Dis. Child. **20**:486 (Dec.) 1920.
20. Jones, H. W.: Lancet **2**:501 (Sept. 4) 1920.
21. Klewitz, F.: Deutsch. Arch. f. klin. Med. **130**:212 (Sept. 26) 1919.
22. Josue, O.: Bull. méd. Par. **34**:391 (April 28) 1920.
23. Lazlett, E. E.: Heart **7**:347 (Aug.) 1920.

practical difference in the predominance of right or left nerve. The right nerve has slight predominant control over the auricular rate, but the left also retards the ventricular rate. The ratio is R : L = 68 : 55. The left vagus is predominant in control of the auriculoventricular conduction, the ratio being R : L = 15 : 23.

Kleemann [24] used Czermak's test pressure on the vagus in 127 patients. Tests on the right vagus showed no effect in 80 out of 150 tests, and on the left vagus no effect in 90 out of 149 tests. Marked modification is only evident in cases of heart disease, but the intensity of the response is not always proportional to the severity of the disease, and a positive response does not always occur with heart disease. When there is partial heart block the response is aggravated. This brings the vagus pressure experiment into the medicolegal realm. Von Teubern [25] points out that in persons with a strongly positive vagus response compression of the throat for a very short space of time, as in attempts to strangle, or choking, may be sufficient to produce immediate arrest of the heart action.

Valsalva's experiment, i.e., forced expiration after deep inspiration with the nose, mouth and glottis closed, according to Maudru [26] gives a chance for better exploration of the heart, because the lungs are still, the heart rate is slower, so that murmurs are more easily studied, and the more intimate contact of the layers of the pericardium may bring out unexpected friction sounds. Dawson and Hodges [27] find that with the Valsalva experiment systolic blood pressure rises rapidly, at first, and this is followed by a marked fall. When the experiment is prolonged the intensity of efforts decreases and with this the changes in the heart rate are less marked. When the Valsalva experiment is interrupted by a series of single gasps, the systolic blood pressure rises from 10 to 20 mm. above the normal. Lifting and "exercises of strain" have this same effect.

The oculocardiac reflex is used for determining the vagus-sympathetic balance. Jenny [28] applied the compression of eyeball test to 250 children whose ages varied from 3 months to 15 years. In only two cases was there a disagreeable effect and the pulse was slowed in all but 4.4 per cent. which included five cases of tuberculous meningitis and two of diphtheria. The oculocardiac reflex is a physiologic reflex which ranks in value with the knee jerk. It tests the vegetative system, and is especially valuable for testing the heart as a control in digitalis treatment. Lesne and Binet [29] induce more vigorous responses in the

24. Kleemann: Deutsch. Arch. f. klin. Med. **130**:221 (Sept. 26) 1919.
25. Von Teubern: Deutsch. med. Wchnschr. **46**:322 (March 18) 1920.
26. Maudru: Paris méd. **10**:504 (July 19) 1920.
27. Dawson, P. M., and Hodges, P. C.: Am. J. Physiol. **50**:481 (Jan.) 1920.
28. Jenny, E.: Arch. f. Kinderh. **68**:64 (Aug. 31) 1920.
29. Lesné, E., and Binet, L.: Arch. de méd. d. enf. **23**:69 (Feb.) 1920.

oculocardiac reflex for testing vagus excitability in children than adults. In infants 2 weeks old, pressure on both eyeballs causes the pulse rate to drop from 120 to 130 down to 90. It returns to normal at once. Guyot and Jeanneney [30] emphasize the need for using caution in applying the test, but find it very valuable in estimating the condition of a patient before operation. If the reaction is normal, the patient may be operated on; if it is inverted it means an upset between the vagus and the sympathetic control, with the sympathetic predominating. This is the condition found in some forms of shock. When the reflex is abolished, there is insufficiency of the medullary centers, and surgery must be cautious.

Prevel [31] speaks of the *abdominocardiac reflex*. This is the acceleration of the heart beat on changing from the reclining to the erect position. There is no alteration in the perfectly healthy person, nor in patients whose abdomen is supported by the abdominal band or by their hands. It is explained by traction from the sagging organs on the solar plexus.

ARRHYTHMIAS

Eyster and Swarthout [32] find that anything that interferes with the normal rate and coordination of the beats interferes with the mechanical efficiency of the heart. Extra systole, always a premature beat, and a deficient beat as compared with the normal, does not markedly reduce the mechanical efficiency; auricular fibrillation and auricular flutter cause a decrease of cardiac output of as much as 34.9 per cent. of the normal; auriculoventricular heart block decreases mechanical efficiency because of the slow ventricular rate. Barlaro [33] insists that treatment of arrhythmias must be based on the special form and the occasional cause such as gastro-intestinal involvement or impacted gallstones. Schrumpf [34] concludes that serious cases of tricuspid insufficiency are nearly always accompanied by complete arrhythmia.

Tachycardia, according to Wilson,[35] in a man who is up and around, is compensatory, pointing to a mild infection with the toxin acting directly on the cardiac vagus. Parxoysmal tachycardia is not incompatable with an active life. Chevallier [36] lists the most common methods of arresting the paroxysms by reflex action. These include swallowing a chunk of bread or drinking in big gulps, taking an emetic to induce

30. Guyot, J., and Jeanneney, G.: J. d. méd. de Bordeaux **91**:591 (Nov. 25) 1920.

31. Prével: Presse méd. **28**:235 (April 21) 1920.

32. Eyster, J. A. E., and Swarthout, E. C.: Arch. Int. Med. **25**:317 (March) 1920.

33. Barlaro, P. M.: Prensa Médica Argentina **6**:231 (Jan. 10) 1920.

34. Schrumpf, P.: Arch. d. mal. du cœur. **12**:529 (Dec.) 1919.

35. Wilson, R. M.: Lancet **1**:146 (Jan. 17) 1920.

36. Chevallier, C.: Bull. méd. Par. **34**:395 (April 28) 1920.

vomiting or tickling the pharynx with a feather, lying on the back and breathing with the chest kept full of air, pressure on the right vagus nerve in the neck, and taking every ten minutes a cachet of pituitary extract. Galli [37] reports an interesting case of paroxysmal tachycardia in which the attack can be produced at will by the giving of atropin.

Paroxysmal auricular fibrillation is found by Mason [38] in 7 per cent. of the cases of auricular fibrillation in the Johns Hopkins Hospital records. The electrocardiograms are given. Willius,[39] studying 500 cases of auricular fibrillation, finds that the mortality in these cases doubles and sometimes trebles that of heart disease not accompanied by this arrhythmia. Levy,[40] in a research on *ventricular fibrillation* in cats and dogs, finds that the ventricle of the cat tends to spontaneous recovery, and this tendency may be aided by massage of the heart and the use of artificial respiration. The time interval between the moment of syncope and the beginning of the massage is not the important factor in recovery. The limitation to the efficiency of massage is the extent of time during which the central nervous system may be deprived of blood (oxygen?) without injury. This is about five minutes as an outside limit in the human brain. The human heart reacts like the cat heart. Ventricular fibrillation in dogs does not tend to spontaneous recovery and is usually fatal, although D'Halluin [41] saved 65 per cent. of the dogs with ventricular fibrillation from exposure to electricity by the intravenous injection of solutions of potassium chlorid.

Esmein [42] collected the recent literature on the pathology of the bundle of His and its ramifications. Schrumpf [43] reports a case of interfering double sinus rhythm the records from which seem to sustain the view that there is a dual action of the right and left nodes of Keith.

Bishop [44] reports an interesting case of *symmetrically placed ventricular extra systoles* and a slow pulse which is very different from true bradycardia in which the pacemaker is slow, or from heart block where impulses do not reach the ventricle. In this case every other normal pulse beat is replaced by a premature contraction which is too feeble to be noticed in the pulse. There is no functional disorder of the mechanism, but each alternating beat is an ectopic beat originating in the ventricle, and is followed by a beat controlled by the normal

37. Galli, G.: Heart **7**:111 (April) 1920.
38. Mason, V. R.: Bull. Johns Hopkins Hosp. **31**:145 (May) 1920.
39. Willius, F. A.: Minnesota Med. **3**:356 (Aug.) 1920.
40. Levy, A. G.: Heart **7**:175 (April) 1920.
41. D'Halluin, M.: Jour. de Radiol. e. d'Electrolog. Paris **4**:254 (June) 1920; Abstr. J. A. M. A. **75**:1297 (Nov. 6) 1920.
42. Esmein, C.: Ann. de Méd. **6**:415 (Dec.) 1919.
43. Schrumpf, P.: Arch. d. mal. du cœur. **13**:168 (April) 1920.
44. Bishop, L. F.: Am. Med. **15**: (new series), April, 1920.

pacemaker. Willius [45] made a study of 277 patients with *bradycardia* and he finds that the causes may be chemical substances, myocardial disease, physiologic changes without cardiac degenerations, early and late asphyxia, and stimulation of the cardiac vagus which gives a temporary bradycardia.

Parkinson, Grosse and Gunson,[46] taking fifty consecutive cases of acute rheumatism, find the myocardium unaltered in only twelve cases. Forty-seven of the patients had a sinus arrhythmia after the attack and 14 per cent. had premature auricular contraction; 30 per cent. had acute heart block, with dropped beats in 8 per cent. Some degree of acute heart block indicating myocarditis is common in acute rheumatism. Goodall,[47] studying twenty cases of *heart block,* points out that rheumatic and syphilitic histories are relatively infrequent. Heart block is almost invariably associated with mitral regurgitation, and pain is a frequent symptom. There is a tendency to sudden death with gastric distention, and Stokes-Adams attacks occur when the heart block is complete. He speaks also of the possibility of transmission of the condition from mother to child.

Eckstein,[48] working on the frog's heart, confirms the view that the width of the impulse conducting tract between the auricle and ventricle does not modify the transmission of the impulse. Partial heart block is not due to the narrowing of the tract. The power of the impulse is dependent on the number of times the elements of the tract can repeat a given process in a given length of time. When two parts with varying lengths of the refractory phase meet there must be arrhythmia—which may be purely functional, due to injurious influences affecting the heart through the blood or nerves or originating within the heart itself. Cases of heart block are reported by Gallavardin and Dumas; [49] Friedlander and Isaacs,[50] whose case shows a dissecting aneurysm of the septum in a man, aged 36; Odriozola,[51] whose case with gumma of the septum shows complete heart block, and a pulse rate dropping to one beat per minute, probably the lowest bradycardia on record; and Pezzi, Donzelot and Yacoel,[52] whose case of complete heart block shows a pulse of auricular origin due to myocardial weakness, in the femoral vein.

45. Willius, F. A.: Arch. Int. Med. **26**:630 (Nov.) 1920.

46. Parkinson, J.; Grosse, A. H., and Grunson, E. B.: Quart. J. Med. **13**:363 (July) 1920.

47. Goodall, J. S.: Lancet **1**:909 (April 24) 1920.

48. Eckstein, A.: Deutsch. Arch. f. klin. Med. **130**:95 (Aug. 15) 1919.

49. Gallavardin, L., and Dumas, A.: Arch. d. mal. du cœur. **13**:63 (Feb.) 1920.

50. Friedlander, A., and Isaacs, R.: J. A. M. A. **75**:1778 (Dec. 25) 1920.

51. Odriozola, E.: An de la Facultad de Med. de Lima **3**:5 (July-Aug.) 1920; abst. J. A. M. A. **75**:1601 (Dec. 4) 1920.

52. Pezzi, C.; Donzelot, E., and Yacoel, J.: Arch. d. mal. du cœur **13**:97 (March) 1920.

Heartblock in children is much more rare. Eyster and Middleton [53] could find only twenty cases of heart block in children in the literature. These were probably either congenital in origin or occurred during severe diphtheria. Their case is in a child, 2 years old, which has been under observation all her life. The lesion at present seems to be a well compensated mitral lesion, with a 2:1 auriculoventricular block, the ventricle rate being from fifty to sixty beats per minute. Carter and Howland [54] report a case of congenital *atrioventricular dissociation* with complete heart block in a child of 5. The auricular rate is 103 and the ventricular rate is 37. There are only seven other established cases of atrioventricular heart block in children. These cases are reviewed in the article.

THE SIZE AND CONTOUR OF THE HEART

Hoover [55] gives the fine distinctions of the lost art of percussion in locating the heart borders. Direct percussion is best for definitive percussion using the terminal phalanx of the extended middle finger, making the blow by firmly stroking, with the patient sitting because the heart is nearer the chest wall. The left cardiac border is located by percussing from the third intercostal space downward; then the upper border by percussing in a line midway between the sternum and the nipple line with the finger parallel to the ribs, downward each costal and intercostal space until there is the characteristic change in note and resistance. The right cardiac borders should be defined by percussing in each right intercostal space from the second to the fifth in succession. The location of the right margin requires all the niceties of technic. Not even the radiographic plate will give the information about flattening of the diaphragm with cardiac enlargement that may be obtained by studying the movement of the costal margins from the subcostal angle to the eighth costal cartilage. For this the patient should be recumbent. Normally, the two sides move symmetrically outward, but if the entire subcostal diaphragm is flattened, the costal margins on both sides from the angle to the eighth rib move less than the lower margins where the lateral phrenic leaves are attached. If the flattening is marked, the costal margins from the angle to the eighth rib move symmetrically inward, and the lower margins move outward, giving an inspiratory narrowing of the subcostal angle. This is a valuable clue to downward enlargement of the heart.

53. Eyster, J. A. E.. and Middleton, W. S.: Am. J. Dis. Child. **19**:131 (Feb.) 1920.

54. Carter, E. P., and Howland, J.: Bull. Johns Hopkins Hosp. **31**:351 (Oct.) 1920.

55. Hoover, F. C.: J. A. M. A. **75**:1626 (Dec. 11) 1920.

Martinet [56] uses the height, the diameter of the chest from axilla to axilla, the transverse diameter and the longest and shortest diameters of the heart. These furnish an index of the relative values of the heart and aorta for different builds, which is very instructive. Cánovas [57] uses a radiocardiometer to measure the ratio between the diameter of the heart and the widest diameter of the chest. Normally, this is almost constant, 25 per cent. of the chest diameter lying to the left of the heart, 42 per cent. being accupied by the heart, and 33 per cent. lying to the right of the heart. Cohn,[58] using the teleroentgen method on soldiers returned from severe active service, finds that their hearts are not larger than the normal.

IRRITABLE HEART AND EFFORT SYNDROME

Warfield and Smith [59] note that cases of *irritable heart* give histories dating back for years—and exercise under observation gives the surest method of separating the fit from the unfit. Galli [60] shows that cardiovascular disease is an inherited tendency, and he gives family trees for "hereditary myocardism." These subjects are unable to stand as much physical exercise as the normal. The heart and aorta are smaller than the average, and the blood pressure is lower. Kerley [61] places the intelligent child, who is unable to apply himself to either mental or physical work because he becomes easily fatigued, in the class of the effort syndrome in children. Schiff [62] reclassifies these children with constitutional inferiority of the circulatory system according to the stability of the vasomotor system. Stolte [63] calls attention to the children whose movements are slow, who do not join in games, who urinate little during the day, but at night when the circulation is relieved pass large amounts of urine. These children may have an indistinct first sound at the apex, or a murmur, which is due to atony of the heart muscles and which disappears as the child grows stronger. The effort syndrome is not heart disease. Meredith,[64] examining 2,000 young women, found 193 who had been told they had valvular lesions who gave no evidence of organic heart disease, but who had a functional disturbance that may be attributed to submyocardial development.

56. Martinet, A.: Presse méd. **28**:302 (May 15) 1920.
57. Cánovas, B. N.: Rev. Española de med. y cir., Barcelona **2**:600 (Nov.) 1919.
58. Cohn, A. E.: Arch. Int. Med. **25**:499 (May) 1920.
59. Warfield, L. M., and Smith, F. M.: J. Lab. & Clin. M. **5**:75 (Nov.) 1919.
60. Galli, G.: Policlinico, Rome **27**:65 (Jan. 19) 1920.
61. Kerley, C. G.: Arch. Pediat. **37**:449 (Aug.) 1920.
62. Schiff, E.: Jahrb. f. Kinderh. **91**:217 (March) 1920.
63. Stolte, K.: Jahrb. f. Kinderh. **92**:1, 1920.
64. Meredith, F. L.: Boston M. & S. J. **181**:734 (Dec. 25) 1919.

ORGANIC HEART LESIONS

White [65] insists on positive evidence for the diagnosis of *heart disease* in young people. This positive evidence consists of definite cardiac enlargement, murmurs that are definitely those of organic valvular lesions, serious arrhythmia such as heart block or auricular fibrillation, congestion of the veins of the neck, enlargement of the liver, edema of the feet and legs, ascites, pulmonary edema and cyanosis. Hewlett [66] adds to this list cardiac infection and alterations in the form of the electrocardiogram. Gibre,[67] from the records on 10,000 recruits with doubtful heart conditions, selects the cases of aortic regurgitation and mitral stenosis. He finds that the most important etiologic factor between the ages of 18 and 41 is rheumatic fever. It is rather surprising to find the statement that there is no evidence here that syphilis, gonorrhea, scarlet fever, diphtheria, or pneumonia are causes of valvular heart lesions. Hall,[68] in 2,500 heart cases, analyzed the 40 per cent. who had valvular heart lesions. Half of these were due to want of tone and to minor causes, all curable with the proper environment.

Of the acute infectious diseases producing heart lesions diphtheria is one of the most important. McCulloch [69] gives the records of eighty cases of diphtheria in children, of whom nineteen showed cardiac disturbance. With lesions of the myocardium and the mechanism, the mortality is 100 per cent. Cardiac failure results the moment the cardiac reserve is used up. The occurrence of *postdiphtheritic myocarditis* is beyond our control, but the outcome may depend on protection given the heart during the disease and convalescence. Aviragnet and Lutembacher [70] report a case of postdiphtheritic derangement of conductivity in a boy, 10 years old. Minet and Legrand [71] report six cases of influenza with heart complications. The prognosis is grave for all organic forms and reserved in all types. Hamburger [72] adds six more cases of *postinfluenzal myocardial involvement*. These may be grouped as (1) fatal cases with acute parenchymatous degeneration and vacuolization of the myocardium, (2) acute nonfatal cases showing involvement of the auricle and the conducting system during the height of the infection and recovery in from two to six weeks, and (3) nonfatal chronic cases with involvement of the auricle and arrhythmia long after subsidence of the acute infection. Acute respiratory infections,

65. White, P. D.: J. A. M. A. **74**:580 (Feb. 28) 1920.
66. Hewlett, A. W.: Northwest Med. **19**:224 (Sept.) 1920.
67. Gibre, C. C.: Brit. M. J. **1**:730 (May 29) 1920.
68. Hall, G. R.: Lancet **1**:1218 (June 5) 1920.
69. McCulloch, H.: Am. J. Dis. Child. **20**:89 (Aug.) 1920.
70. Aviragnet and Lutembacher: Arch. d. mal. de cœur. **13**:197 (May) 1920.
71. Minet and Legrand: Paris méd. **10**:133 (Feb. 14) 1920.
72. Hamburger, W. W.: Am. J. M. Sc. **160**:479 (Oct.) 1920.

such as influenza and streptococcus lesions, seem to single out the auricle and the conduction pathways. Oliverira [73] finds that lung processes, especially fibrous degeneration of the lung, cause disturbances in the venous cardiovascular system which are slowly progressive and lead up to auricular fibrillation. This correlation between auricular fibrillation and the pulmonary condition is the basis for his term—*pulmonary heart*.

Williamson [74] injects a warm gelatin and agar mixture into the pericardial sac of fresh cadavers, to study *pericarditis with effusion*. The fluid accumulates first along the lower margin of the heart and about the apex; with larger effusions it collects next over the large vessels of the base. This collection is independent of position. In almost every case this pushes down the diaphragm and the left lobe of the liver. Even in large effusions the anterior surface of the heart may remain uncovered so that a pericardial friction rub may still be noted. Percussion dullness in the right fifth interspace, or rounding of the cardiohepatic angle is not demonstrable in experimental pericardial effusions. Holden [75] reports three cases with abdominal symptoms and laparotomy —in which the lesion was a pericarditis. Rehn [76] treats *adhesive pericarditis* by splitting the sternum, slitting the pericardium, and breaking up the adhesions. Four cases in children showed immediate improvement, and recovery from the operation, but two died soon afterward of tuberculosis elsewhere, one after eighteen months of influenza, and one after one year of acute rheumatism.

Dwyer [77] cites a case of *ulcerative endocarditis* in a child, 23 months old, due to the gonococcus. In over 600 cases of endocarditis in children there is only one mention of endocarditis due to the gonococcus. The most common agent is *Streptococcus viridans*. This was found in the case of Kretschmer and Conboy [78] in which both the aortic and mitral valves were perforated. Münzer [79] thinks that the presence of streptococci in the blood does not justify prognostic conclusions; that chills and splenic enlargement are more important for a bad prognosis. Baehr and Lande [80] believe that the glomerulonephritis which is the cause of death in 11.5 per cent. of their cases of subacute streptococcus endocarditis is initiated only during the bacteremia in the acute stage of

73. De Oliverira, O.: An. de la Facult. de Med. Montivideo **5**:297 (July-Aug.) 1920; Abstr. J. A. M. A. **75**:1808 (Dec. 25) 1920.
74. Williamson, C. S.: Arch. Int. Med. **25**:206 (Feb.) 1920.
75. Holden, W. B.: Northwest. Med. **19**:230 (Sept.) 1920.
76. Rehn, L.: Arch. f. Kinderh. **68**:179 (Oct. 16) 1920.
77. Dwyer, H. L.: J. A. M. A. **75**:1643 (Dec. 11) 1920.
78. Conboy, J. E., and Kretschmer, H. L.: J. A. M. A. **74**:154 (Jan. 17) 1920.
79. Münzer, E.: Zentralbl. f. inn. Med. **41**:282 (April 17) 1920.
80. Baehr, G., and Lande, H.: J. A. M. A. **75**:789 (Sept. 18) 1920.

endocarditis. Cotton [81] analyzes the clinical symptoms and complications in subacute endocarditis. Thomas and O'Hara [82] report a case of endocarditis of the tricuspid valve due to the pneumococcus, Type I. Hannemann [83] finds that the warty efflorescences in endocarditis are made up of valvular tissue and are not superficial deposits, the deposit of cells arising from the valvular tissue and not from leukocyte accumulations.

Kaufmann,[84] studying *large hearts* in soldiers, finds that most of these are not hypertrophied. The power of dilation is a compensating heart mechanism, but the larger the heart the less the relief from dilation. The amount of strain depends on the previous condition of the heart and not the severity of the exercise. Of one group of fifty men showing no disordered heart action after two years at the front, only eight had had acute infections after the age of 14; while in another group of fifty men who were returned with severe heart symptoms after five months at the front, thirty-seven had had acute infections after the age of 14. Acute dilatation of the heart during or following surgical operation, in nine cases reported by Levine,[85] showed abnormal mechanism of the heart beat, with the changes in the auricular beat. Esmein [86] finds that the auriculoventricular valves are more apt to become insufficient with dilatation which really lightens the work of the heart. Wilson [87] says that every case of cardiac decompensation without valvular lesions must be considered a case of chronic myocarditis. Leon [88] and Morquis [89] report cases occurring in children in which a toxic action in the myocardium and compensatory dilatation caused a *gallop sound* which directed the attention to an acute nephritis. Lian [90] considers the *third heart sound* physiologic, and Pezzi [91] opposes the view that a double crural sound is a symptom of aortic insufficiency. It is of mixed arterial and venous origin, is never present with compensated aortic insufficiency, and it occurs only with myocardial weakness.

81. Cotton, T. F.: Brit. M. J. **2**:851 (Dec. 4) 1920.

82. Thomas, H. M., Jr., and O'Hara, D.: Bull. Johns Hopkins Hosp. **31**: 417 (Nov.) 1920.

83. Hannemann, E.: Virchows Arch. f. path. Anat. **226**: Supp. 138-149, 1919; Abstr. Bacteriol. **3**: (Dec.) 1919.

84. Kaufmann, R.: Wien. Arch. f. inn. Med. **1**:211 (June) 1920.

85. Levine, S. A.: J. A. M. A. **75**:795 (Sept. 18) 1920.

86. Esmein, C.: Médecine, Paris **1**:336 (March) 1920.

87. Wilson, F. N.: Mississippi State M. A. J. **17**:403 (Oct.) 1920.

88. Ponce de Leon: Arch. Latino-Amer. de Pediat., Buenos Aires **14**:266 (May-June) 1920.

89. Morquis, L.: Arch. Latino-Amer. de Pediat., Buenos Aires **13**:424 (Oct.) 1919.

90. Lian, C.: Médecine, Paris **1**:333 (March) 1920.

91. Pezzi, C.: Arch. d. mal du cœur **12**: (Dec.) 1919.

Rosenbaum,[92] studying *cardiac complications in scarlet fever,* finds myocarditis common in the latter part of the acute stage and in convalescence, but a pre-existing old heart lesion does not mean a bad prognosis in scarlet fever. Whitman and Eastlake[93] trace all stages from muscle cell to Aschoff cells in rheumatic myocarditis. The myocardial rheumatic nodule, or Aschoff body, is made up of large elements arranged radially about a center. The cells are similar to epithelioid cells, but larger like the giant cells in Hodgkin's disease. They are round, fusiform or oval, often multinuclear. The nodules lie close to small blood vessels and are surrounded by a zone containing polymorphonuclear leukocytes, plasma cells and lymphocytes.

Norton[94] reports a case of myxoma of the heart in the hope of finding a symptom complex for *cardiac tumors.* Rutherford[95] reports a case of *cardiac angina in a child,* with a review of the literature of angina pectoris and degenerations in the aorta in children. Lutembacher[96] cites three cases of aneurysm of the left ventricle in adults. Reid[97] reports an experimental study on dogs with experimental *arteriovenous fistulae.* There is a marked tendency for such experimental fistulae to close.

WOUNDS OF THE HEART

Mocquot and Constantini[98] report eleven cases in which the heart wound in the ventricle is plugged with a clot, and may heal spontaneously, although if this clot becomes destroyed, there may be secondary hemorrhage and delayed symptoms. Collins[99] sutured the heart in a case of gunshot wound of the left ventricle. The man lived thirteen days, and died of the effect of exposure due to an attempted escape from the hospital. At necropsy the heart and pericardium were completely healed. Proust[100] records the results of a re-examination ten years after suture of the heart, in which the heart is apparently normal. In the discussion of this paper Josue gives the findings in ten cases in which there were operations on the heart after war wounds.

CONGENITAL ANOMALIES OF HEART AND CIRCULATION

Vaquez and Donzelot[101] distinguish between *dextrocardia* and

92. Rosenbaum, H. A.: Arch. Int. Med. **26**:424 (Oct.) 1920.
93. Whitman, R. C., and Eastlake, A. C.: Arch. Int. Med. **26**:601 (Nov.) 1920.
94. Norton, W. H.: Am. J. M. Sc. **158**:689 (Nov.) 1919.
95. Rutherford, W. J.: Brit. J. Child. Dis. **17**:22 (Jan.-March) 1920.
96. Lutembacher, R.: Arch. d. mal. du cœur **13**:49 (Feb.) 1920.
97. Reid, M. R.: Bull. Johns Hopkins Hosp. **31**:43 (Feb.) 1920.
98. Mocquot, P., and Constantini: Rev. de chir. **39**:257, 1920.
99. Collins, A. W.: J. A. M. A. **75**:1271 (Nov. 6) 1920.
100. Proust: Bull. et mém. Soc. méd. d. hôp. de Par. **44**:1035 (July 16) 1920.
101. Vaquez, H., and Donzelot, E.: Presse méd. **28**:41 (Jan. 17) 1920.

dextroversion; one, the mirror aspect, being merely a mechanical displacement and the other, inversion of the cavities, is an abnormal embryonal development. Parsons-Smith [102] shows that dextrocardia with complete transposition of the organs—situs inversus totalis—does not incapacitate, but incomplete transposition is usually accompanied by actual malformations of the heart and of the body. Schüssler's [103] case had supernumerary vertebrae; Moncalvi's [104] case with situs inversus and dextrocardia has congenital stenosis of pulmonary, and probably, a patent ductus arteriosus; Ochsenius [105] reports the fifth case in the literature of *familial situs inversus totales* in non twins.

Goehring [106] reports a case of *anuerysm of the postaortic sinus of Valsalva* of congenital origin, which clinically gave signs of tricuspid insufficiency. Rupture resulted in death. There are only six such cases on record. Plowden [107] reports a case of congenital malformation of the heart in which there is no pulmonary artery, but there is a large abnormal branch arising from the arch of the aorta. Toy and Ellis [108] also report a case with absence of the pulmonary artery and other defects. McLean [109] has a case of congenital heart disease that cleared up in five years. He suggests that there might have been a defect in the ventricular septum, and that there has been a return to normal rather than compensation.

Weber,[110] studying sixty-two cases of congenital heart defect, finds that there is no characteristic stunting of growth or malnutrition. Children with congenital cyanosis and with dyspnea are, however, more subject to deranged nutrition.

INCIDENCE OF HEART DISEASE AND THE CARE OF CARDIAC PATIENTS

Hoffman [111] collected the statistics on heart disease. The relative frequency of valvular heart disease and endocarditis in men of military age is 2.6 per cent.; and of all forms of heart disease leading to total rejections is 3 per cent.—about the same as pulmonary tuberculosis. Conner [112] gives heart defects as causing a rejection rate of 4.25 per cent. in the army, while in 1917 the death rate in the United States registration area from heart disease was 12.1 per cent. of the total.

102. Parsons-Smith, B.: Lancet **2**:1076 (Dec. 13) 1919.
103. Schüssler, O.: Deutsch. med. Wchnschr. **46**:658 (June 10) 1920.
104. Moncalvi, M.: Pediatria, Naples **28**:907 (Oct. 1) 1920.
105. Ochsenius, K.: Monatschr. f. Kinderh. **19**:27 (Oct.) 1920.
106. Goehring, G.: J. M. Res. **42**:49 (July-Sept.) 1920.
107. Plowden, H. H.: South Carolina M. A. J. **15**:649 (Dec.) 1919.
108. Toy, W. B., and Ellis, A. G.: J. A. M. A. **74**:322 (Jan. 31) 1920.
109. McLean, S.: J. A. M. A. **74**:1229 (May 1) 1920.
110. Weber, O.: Monatschr. f. Kinderh. **18**:205 (June) 1920.
111. Hoffman, F. L.: J. A. M. A. **74**:1364 (May 15) 1920.
112. Conner, L. A.: J. A. M. A. **74**:1564 (June 5) 1920.

There is no doubt that the cardiac patients need special care and attention. Conner outlines the growth of cardiac clinics and institutions for the care of heart cases in New York City. In 1911 there was a single outpatient heart clinic in Bellevue hospital, while in 1920 there were twenty-seven cardiac dispensary classes, accommodating 3,000 persons, convalescent homes for heart cases, inspection and care of children with crippled hearts, and special classes for these children, and occupational work under supervision of the Employment Bureau for the Handicapped. St. Lawrence and Adams [113] report in detail the care of cardiac children, with the object of making them useful citizens. Duggan [114] reports from the Employment Bureau for the Handicapped the results of placing cardiac patients and the types of employment suitable for cardiac patients. One difficulty seems to be assuring the employer that the workman with a heart lesion will not drop dead suddenly.

LESIONS OF THE AORTA

Martin [115] lists as causes for widening of the shadow of the great vessels chronic mitral lesions with dilated pulmonary artery, congenital heart lesions, long continued hypertension, a high diaphragm, arteriosclerosis and syphilitic aortitis. Brown [116] calls attention to retrosternal pain as an important symptom of acute aortic dysfunction, the prognosis of which is not necessarily grave in young persons. Stolkind [117] is unable to find in the literature a single case of proved *hereditary syphilitic aortitis* in older children, adolescents and adults, although such cases may exist. About seventy-five cases are on record of aortic changes in new-born infants with hereditary syphilis, and the pathologic findings are different from syphilitic aortitis in adults. The literature on the finding of *Spirochaeta pallida* in the tissues of children is also reviewed. Martinet [118] finds only five cases in his series of patients with aortic aneurysm whose histories exclude the possibility of syphilis.

Moon [119] reports a case of congenital stenosis of the aorta in a boy, 11 years old, who is active, energetic and bright, but somewhat undersized and pale.

THE CAPILLARIES

The conception of the capillaries has undergone a radical change in the past two years. Since about 1860, vasomotor changes have been considered synonymous with arteriomotor—a function of blood pres-

113. St. Lawrence, W. P., and Adams, E.: Hosp. Service Quart. **2**:151 (May) 1920. Quoted from Editorial, J. A. M. A. **75**:609 (Aug. 28) 1920.
114. Duggan, I. M.: Cardiac Hosp. Soc. Serv. Quart. **2**:229 (May) 1920.
115. Martin, C. E.: J. A. M. A. **74**:723 (March 13) 1920.
116. Brown, G. E.: Ann. Med. **1**:242 (July) 1920.
117. Stolkind, E. J.: Brit. J. Child. Dis. **17**:126 (Sept.) 1920.
118. Martinet, A.: Presse méd. **28**:733 (Oct. 16) 1920.
119. Moon, R. O.: Lancet **1**:1314 (June 19) 1920.

sure. The pumping mechanism [120] is not the sole factor in blood distribution—the peripheral vasomotor changes must be considered. The vasomotor control was formerly considered due to vasoconstrictor and vasodilator nerves, but more recently the possibility of chemical control—sensibility to cellular products has been discussed. Hooker [121] examines the capillaries and venules in the cat's ear, and finds that there is a definite *"capillariomotor" mechanism* which is subject to chemical and to nervous control. Baylis [122] says that the absence of a muscular coat does not rule out the possibility of active changes in the capillaries, and Krogh [123] says they function in active dilatation and there is capillary tone. In another article, Krogh [124] shows that the capillariomotor mechanism in the frog is only slightly dependent on the nerve supply, and that maintenance of the capillary tonus is dependent on the blood supply. With a lowered blood supply, the tonus diminishes, causing relaxation and the admission of a current of blood and tone is regained. The substance responsible for tonus in the blood is not known, but it is not oxygen supply. These experiments recall the old findings of Cushing on examining the capillaries in the meninges of the monkey through a trephine opening, and discovering that normally the capillaries are not continuously filled with blood, but that the filling comes in waves, or pulsations. Dale [125] accepts the view of actively contractile capillaries, and thinks this will play a part of increasing importance in the conception of the mechanism for regulating blood supply and in the explanation of shock. Wolfer [126] notes that the intrapulmonary circulation and the body circulation balance, supplement and compensate each other, and different drugs act differently on the two, epinephrin causing the vessels of the pulmonary circulation to dilate.

Danzer and Hooker [127] determine the *capillary blood pressure* with the microcapillary tonometer which fits on a microscope stage, and the pressure is applied through a capsule with a transparent membrane through which the skin is observed under the microscope with a magnification of 70x. The criterion for reading is the point where stagnation occurs. The normal pressure is 22.2 mm. Hg and there is slight diurnal variation. Kylin [128] uses the same type of apparatus and finds that in 100 healthy subjects the capillary blood pressure range is 110-190 mm. water. The arterial hypertension cases fall into two groups, one

120. Editorial, J. A. M. A. **75**:1784 (Dec. 25) 1920.
121. Hooker, D. R.: Am. J. Physiol. **54**:30 (Nov.) 1920.
122. Editorial, J. A. M. A. **74**:178 (Jan. 17) 1920.
123. Krogh, A.: J. Physiol. **52**:457, (May) 1919.
124. Krogh, A.: J. Physiol. **53**:399 (May) 1920.
125. Dale, H. H.: Bull. Johns Hopkins Hosp. **31**:256 (Aug.) 1920.
126. Wolfer, P.: Cor.-Bl. f. schweiz. Aerzte **49**:1817 (Nov. 27) 1919.
127. Danzer, C. S., and Hooker, D. R.: Am. J. Physiol. **52**:136 (May) 1920.
128. Kylin, E.: Zentralbl. f. inn. Med. **41**:505 (July 18) 1920.

with increased capillary blood pressure, and the other without any increase in the capillary pressure. The last group includes the benign nephroses.

BLOOD PRESSURE

An editorial in the *Journal of the American Medical Association* [129] calls attention to the change in the conception of the normal blood pressure: eight years ago from 150 to 160 mm. of mercury was taken as the upper limit of normal systolic blood pressure; two years later the age factor was more clearly recognized and systolic pressures over 135 mm. were considered as hypertension in persons under middle age. Alvarez [130] fixes the normal from studies made on freshmen at the University of California as from 85 to 155 mm. for women and from 90 to 175 mm. for men. In women there is a decrease in blood pressure between the ages of 17 and 25, and in men between the ages of 17 and 21. Kahn [131] shows that the normal varies with the position of the arm, both systolic and diastolic pressures decreasing as the arm is raised. For comparable results all readings should be taken with the arm at the side.

Miller [132] studies blood pressure changes of interest to surgeons..

TABLE 1.—SYSTOLIC BLOOD PRESSURE VARIATIONS DUE TO POSITION
(1,000 CASES)

Position	Variation Less Than 10 Mm., per Cent.	Blood Pressure Diminished, per Cent.	Blood Pressure Increased, per Cent.	Tendency to
Dorsal................................	55	22.5	22.5	Remain normal
Lithotomy............................	64.5	11.1	24.4	Remain normal
Trendelenburg.......................	38.7	57.2	4.1	Diminish
Combined lithotomy and Trendelenburg.........................	25	25	50	Increase

A drop in temperature in the operating room is followed by a fall in blood pressure which is more marked when there is visceral exposure. The temperature of the operating room should never be below 70 F. in major operations. A quiet anesthesia shows no blood pressure change; a deep anesthesia is apt to give a rapid decline in blood pressure, and spinal anesthesia may give a drop that reaches the danger zone.

Cordier [133] believes that localized hypertension in the hands and feet, which occurs spasmodically without any trophic disturbance, is the first

129. Editorial, J. A. M. A. **75**:1650 (Dec. 11) 1920.
130. Alvarez, W. C.: Arch. Int. Med. **26**:381 (Oct.) 1920.
131. Kahn, M. H.: Am. J. M. Sc. **158**:823 (Dec.) 1919.
132. Miller, A. H.: J. A. M. A. **74**:514 (Feb. 21) 1920 .
133. Cordier, V.: Arch. d. mal. du cœur **13**:241 (June) 1920.

stage of a phenomenon to be noted in the next ten years when this present generation will present heart and kidney conditions due to the intoxications, fatigues and latent infections of the recent war campaigns.

There is a group of three papers on *blood pressure changes in pulmonary conditions.* Amblard [134] in acute pulmonary edema finds a high blood pressure, running higher during the development; then, as the ventricle gives way, there is a sudden drop, which is followed by edema. The heart action keeps up and no arrhythmia develops. Edgeworth [135] finds that in 3 per cent. of the cases of lobar pneumonia death results from a persistent fall in blood pressure. De Bloeme,[136] studying 500 cases of pulmonary tuberculosis, finds that the blood pressure is normal in 87.7 per cent. during the first stage, in 86 per cent. during the second stage and in 75 per cent. during the third stage. Only the third stage shows a marked tendency toward a falling pressure almost 18 per cent. having subnormal pressures. Cases with a low blood pressure—from 80 to 100 mm.—all terminate fatally in less than one year.

The correlation of *endocrine dyscrasias and blood pressure changes* are studied by Engelbach [137] who analyzed 500 uncomplicated endocrine cases. Ten per cent. of the cases showed increased blood pressure, the highest pressures occurring in the 30 per cent. of these cases representing pluriglandular dycrasias; pituitary, thyroid, and ovarian changes come next in frequency as causing increased blood pressures. The prognosis in endocrine hypertension is more favorable than in vasculorenal hypertension. Downs [138] finds that splenic and thymic substances do not affect the blood pressure in dogs; ovarian and thyroid substances cause oscillation in the pressure; mammary gland substance first increases, then lowers the pressure; pancreatic substance and secretin lower the blood pressure while epinephrin raises it. Sandiford,[139] giving 0.5 c.c. of a 1 :1000 solution of epinephrin chlorid gets an increase in systolic and a decrease in diastolic blood pressures. Schiff and Epstein [140] find that normal children respond to epinephrin with a considerable increase in blood pressure that is uninfluenced by change in position. Children with weak pulse and low tension may give little, if any, response to epinephrin, but if the vasomotor system is stable, the pressure rises on reclining. Children with unstable innervation usually give a prompt but slight rise in blood pressure which is not altered by

134. Amblard, L.: Paris méd. **10**:425 (May 22) 1920.
135. Edgeworth, F. H.: Bristol M.-Chir. J. **37**:86 (June) 1920.
136. de Bloeme, P. J.: Nederlandsch Tijdschr. v. Geneesk. **1**:943 (March 29) 1920; Abstr. J. A. M. A. **75**:1238 (Oct. 30) 1920.
137. Engelbach, W.: J. A. M. A. **74**:1619 (June 12) 1920.
138. Downs, A. W.: Am. J. Physiol. **52**: (July) 1920.
139. Sandiford, I.: Am. J. Physiol. **51**:407 (April) 1920.
140. Schiff, E., and Epstein, B.: Jahrb. f. Kinderh. **91**:128 (Feb.) 1920.

change in position. Lowry and Wright [141] find that the injection of epinephrin in dementia praecox cases does not give data of value in the differential diagnosis. Weber [142] calls attention to high blood pressure as a diagnostic sign in suprarenal tumors; one child 5 years old having a systolic pressure of 108 mm. Hg.

PULSE AND BLOOD PRESSURE

Sahli [143] considers that blood pressure determinations are misleading unless the pulse volume is determined at the same time. Sewall [144] suggests that estimations should be made, under different conditions, of the velocity of the blood current as represented by the product of the pulse pressure multiplied by the pulse rate.

Dawson [145] finds that physical training slows the pulse rate, increasing the diurnal variation in pulse rate; increasing the systolic pressure and decreasing the diastolic pressure thus increasing the pulse pressure. Building from Dreyer's foundation that the heart rate of the wild hare which leads an active life is 68 compared to a heart rate of 200 in the rabbit which lives an inactive life, and that wild hare's blood volume is three times the blood volume of the rabbit; and from Boney's work showing that with fatigue there is a difference in the pulse rate on standing and lying down, Schneider [146] tabulates the changes into a point system with plus and minus ratings. A score of 9 or less is characteristic of physically unfit men.

Wilson [147] tested twenty average normal children for their *circulatory reactions to graded exercises.* Immediately after exercise the pulse rate is markedly increased but in 86 per cent. it returns to normal or below normal in two minutes. The systolic pressure with moderate exercise rises to the summit in from twenty to forty seconds and falls to the pre-exercise level in two minutes. With severe exercise, the height of the rise is increased reaching a maximum in from fifty to seventy seconds, and falling more slowly, taking from three to five minutes to reach the pre-exercise level showing that the exercise tolerance of the child has been reached or passed. Mabon [148] studying changes in the blood pressure and pulse in fifty patients with effort syndrome finds that the amount of work they are able to accomplish before fatigue occurs is much less than the normal, but the pulse changes and blood pressure changes are not abnormal.

141. Lowry, L. G., and Wright, W. W.: Boston M. & S. J. **183**:209 (Aug. 12) 1920.
142. Weber, F. P.: Practitioner, London **105**:181 (Sept.) 1920.
143. Sahli, H.: Schweiz. med. Wchnschr. **50**:2 (Jan.) 1920.
144. Sewall, H.: Am. J. M. Sc. **108**:786 (Dec.) 1919.
145. Dawson, P. M.: Am. J. Physiol. **50**:443 (Dec.) 1919.
146. Schneider, E. C.: J. A. M. A. **74**:1506 (May 29) 1920.
147. Wilson, M. G.: Am. J. Dis. Child. **20**:188 (Sept.) 1920.
148. Mabon, T. M.: Am. J. M. Sc. **158**:818 (Dec.) 1919.

TABLE 2.—Points for Grading Cardiovascular Changes
(Schneider's Table)

A. Reclining Pulse Rate		B. Pulse Rate Increase on Standing				
Rate	Points	0–10 Beats, Points	11–18 Beats, Points	19–26 Beats, Points	27–34 Beats, Points	35–42 Beats, Points
50– 60	3	3	3	2	1	0
61– 70	3	3	2	1	0	—1
71– 80	2	3	2	0	—1	—2
81– 90	1	2	1	—1	—2	—3
91–100	0	1	0	—2	—3	—3
101–110	—1	0	—1	—3	—3	—3

C. Standing Pulse Rate		D. Pulse Rate Increase Immediately after Exercise				
Rate	Points	0–10 Beats, Points	11–20 Beats, Points	21–30 Beats, Points	31–40 Beats, Points	41–50 Beats, Points
60– 70	3	3	3	2	1	0
71– 80	3	3	2	1	0	0
81– 90	2	3	2	1	0	—1
91–100	1	2	1	0	—1	—2
101–110	1	1	0	—1	—2	—3
111–120	0	1	—1	—2	—3	—3
121–130	0	0	—2	—3	—3	—3
131–140	—1	0	—3	—3	—3	—3

E. Return of Pulse Rate to Standing Normal after Exercise		F. Systolic Pressure, Standing, Compared with Reclining	
Seconds	Points	Change in Mm.	Points
0– 60	3	Rise of 8 or more	3
61– 90	2	Rise of 2–7	2
91–120	1	No rise	1
After 120: 2– 10 beats above normal	0	Fall of 2–5	0
After 120: 11– 30 beats above normal	—1	Fall of 6 or more	—1

May [149] and Lereboullet and Heitz [150] discuss the Pachon oscillometer, which gives valuable information by the amplitude of the oscillation. Lereboullet and Heitz say that it reveals apparent death in the new-born, shows maximal and minimal blood pressure, the condition of the peripheral circulation and the relative vasoconstriction of different arteries. May says the ocillometer index (amplitude of vibration) is the result of different factors, and that dividing this index by the difference between the maximal and minimal pressure gives an oscillometer ratio which is a true record of the vascular elements of the pulse.

BLOOD VOLUME

Löwy,[151] using Bangs micromethod, determines the *sodium chlorid content of capillary blood* and then injects 400 c.c. of isotonic glucose solution intravenously. Immediately afterward, and sometimes five or ten minutes later, the sodium chlorid value is again determined. Then the total blood volume $= \frac{a_2 b}{a_1 - a_2}$ where a_1 equals the salt content before infusion; a_2 the salt content after infusion; and b the amount of

149. May, E.: Presse méd. **28**:423 (June 26) 1920.
150. Lereboullet, P., and Heitz, J.: Paris méd. **10**:1 (July 3) 1920.
151. Löwy, J.: Zentralbl. f. inn. Med. **41**:337 (May 8) 1920.

fluid infused. The total blood volume normally is from one-eighteenth to one-twelfth of the total weight. Löwy gives the error of the method as not being over 5 per cent. Boenheim and Fischer [152] consider Löwy's principle as good but say that the method used for the sodium chlorid determination is not accurate enough to give even approximate results. In a series of four studies on blood volume, Hooper, Smith, Belt and Whipple; [153] Dawson, Evans and Whipple; [154] and Smith,[155] determined the soundness of the dye blood volume method which has an error of not more than 5 per cent.; and the behavior of a series of dyes, selecting vital red as the one for use. McQuarrie and Davis [156] outline a method of reading refractometrically the serum protein increase after injecting a known amount of gelatin or acacia solutions. This method has the advantage of not being affected by hemolysis, cholemia or lipemia. Harris [157] suggests substituting congo red for vital red because the sodium salt of congo red is red, and the free acid form is blue. Changing it to blue for color comparison rules out any effect from hemolysis. The optimal interval for the withdrawal of blood after injection of dye is about twice the circulation time or two and one half minutes for man. His formulas are:

$$\text{Volume of plasma} = \frac{\text{Dilution factor} \times \text{No. of C.c. of dye injected}}{\text{Ratio of strength of dye in plasma}}$$

$$\text{Volume of blood} = \text{volume of plasma} \frac{100 \text{ per cent.}}{\text{Per cent. of plasma by hematocrit}}$$

Weight of blood = volume × specific gravity.

Salvesen [158] finds that the average blood volume in six healthy young subjects is 5.95 c.c. per 1,000 gm. of body weight or from one-fourteenth to one-nineteenth of the body weight.

Plesch [159] determines the *volume of blood discharged during phases of the heart cycle* by the amount of oxygen given off by arterial blood. The oxygen consumption is determined by the respiratory metabolism; the amount of oxygen held in the blood by a special type of hemoglobinometer, and then the oxygen content of blood from heart by the rubber bag apparatus.

152. Boenheim and Fischer: Zentralbl. f. inn. Med. **41**:553 (Aug. 7) 1920.
153. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Am. J. Physiol. **51**:205 (March) 1920.
154. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: Am. J. Physiol. **51**:232 (March) 1920.
155. Smith, H. P.: Ibid. p. 221.
156. McQuarrie, I., and Davis, N. C.: Ibid. p. 257.
157. Harris, D. T.: Brit. J. Exper. Path. **1**:142 (June) 1920.
158. Salvesen: J. Biol. Chem. **40**:109 (Nov.) 1919.
159. Plesch, J.: Deutsch. med. Wchnschr. **45**:1401 (Dec. 18) 1919.

BLOOD CONCENTRATION

Rubow [160] by restricting the fluid intake to about one-third of the twenty-four hour requirement, reduces the water content of the blood as much as 12.5 per cent. in a few days. Rominger [161] finds that the water content in the blood of infants is remarkably stable. Water passes readily from the stomach to the blood, but with the exception of decomposition cases the hydremia is transient.

Blood concentration means a failing circulation, an inefficient oxygen distribution, oxygen starvation, decreased temperature and finally death. In influenza, while edema of the lungs is indirectly concerned, Underhill and Ringer [162] believe that blood concentration is the immediate cause of death. The hemoglobin content is used as an index of concentration, and treatment to combat the concentration should be begun before the blood concentration has reached 125 per cent. of the individuals normal hemoglobin value. Wilson and Goldschmidt [163] believe that the loss of water from the blood in the development of lung edema is the cause of blood concentration and not imbibition of water by tissues as a result of oxygen want. Hill's [164] views oppose those of Wilson and Goldschmidt, but stagnation is considered the factor in causing oxygen want.

Lutz and Schneider [165] find that the cardiac and respiratory centers are stimulated by a decrease in oxygen and inhibited by an increase in oxygen. The heart responds in from five to fifty-five seconds to an oxygen decrease. Barcroft [166] divides *anoxemia* into three types, (a) the anoxic type with general condition low and low oxygen pressure, (b) the anemia type gaged by the quantity of oxygen liberated from the blood, and (c) the stagnant type with increased hemoglobin.

THE ACID-BASE EQUILIBRIUM AND ALKALI RESERVE

Studies on the alkali reserve and the acid-base equilibrium have been fewer in number during the past year and there has been more of an attempt made to establish normal and comparable values. Collip [167] finds that alkali reserve is either unaltered or diminished during sleep. Haskins and Osgood [168] use the Van Slyke titration method as a class room method, but find that students have difficulty in matching a clear

160. Rubow, V.: Hospitalstidende **63**:305 (May 19) 1920; Abstr. J. A. M. A. **75**:514 (Aug. 14) 1920.

161. Rominger, E.: Ztschr. f. Kinderh. **26**:23 (July 28) 1920.

162. Underhill, F. P., and Ringer, M.: J. A. M. A. **75**:1531 (Dec. 4) 1920.

163. Wilson, D. W., and Goldschmidt, S.: Am. J. Physiol. **50**:157 (Oct.) 1919.

164. Hill, L.: Lancet **1**:359 (Feb. 14) 1920.

165. Lutz, B. R., and Schneider, E. C.: Am. J. Physiol. **50**:327 (Dec.) 1919.

166. Barcroft, J.: Lancet **2**:485 (Sept. 4) 1920.

167. Collip, J. B.: J. Biol. Chem. **41**:473 (April) 1920.

168. Haskins, H. D., and Osgood, E. F.: J. Lab. & Clin. M. **6**:37 (Oct.) 1920.

phosphate standard with the turbid plasma, so they add raw starch to the standard, making it also turbid, and the students get better results. Haggard,[169] in a paper forming a portion of the studies on hemato-respiratory functions, reports that an increase in the body temperature lowers the alveolar carbon dioxid tension and reduces the amount of carbon dioxid in the blood. No compensatory changes occur in the carbon dioxid combining power of the blood. The alkali in use is not lowered in proportion to the decrease in the carbon dioxid dissolved so that the $C_2H_2O : NaHCO_3$ ratio is lowered and presumably the C_H value is lowered. Haggard and Henderson,[170] in three papers in the same series of studies, find that with low oxygen, over-breathing occurs before the blood alkali is appreciably reduced. Intravenous injection of lactic acid does not induce an acidosis at all commensurate with the amount administered, and an increase in the lactates in the blood or urine is probably an indication of a low $C_2H_2O : NaHCO_3$ ratio. Over-breathing throws off an excess carbon dioxid bringing the carbon dioxid ratio below normal. This alkalosis is compensated by the disappearance of alkali from the blood. The process is reversed by normal oxygen tension and acidosis recalls the alkali to the blood. The barometric pressure to which one is acclimated is the fundamental factor controlling the volume of air breathed per unit mass of carbon dioxid eliminated, the alveolar carbon dioxid tension, and the amount of alkali called into use in the blood. Haggard [171] finds that the corrections in the Henderson-Morris method for determining carbon dioxid in plasma and whole blood almost exactly neutralize each other and the gas burette readings may be taken direct each 0.01 c.c. $=$ 1 volume per cent. of carbon dioxid.

Collip and Backus [172-173] finds that the carbon dioxid combining power of the plasma is an approximate index of the alkali reserve of the body fluids in normal animals. The C_H of the spinal fluid is protected to a greater degree than that of blood; the carbon dioxid combining power of spinal fluid as compared with plasma is at a high level in shock. Forced breathing washes out the carbon dioxid from the blood, but the tissues give a buffer reaction, taking up alkali, which accounts for the rapid return to normal when the forced breathing stops. The tetany and muscle cramps developing during hyperpnea would appear to be due to tissue alkalosis. Grant and Goldman's [174] experiments seem to substantiate this view.

169. Haggard, H. W.: J. Biol. Chem. **44**:131 (Oct.) 1920.
170. Haggard, H. W., and Henderson, Y.: J. Biol. Chem. **43**:15 (Aug.) 1920.
171. Haggard, H. W.: J. Biol. Chem. **42**:237 (June) 1920.
172. Collip, J. P., and Backus, P. L.: Am. J. Physiol. **51**:551 (April) 1920.
173. Collip, J. P., and Backus, P. K.: Ibid. p. 568.
174. Grant, S. B., and Goldman, A.: Am. J. Physiol. **52**:209 (June) 1920.

The *effect of hemorrhage on the alkali reserve* is studied by Buell [175] who finds that the drop in alkali reserve is slight if the animal is quiet; and by Tatum [176] who believes that a change in the acid-base balance in the body cells is responsible for rise in blood sugar after hemorrhage. *Ether anesthesia affects alkali reserve.* Carter [177] finds that the carbon dioxid combining capacity of dog's blood diminishes after the first hour of anesthesia, the amount being in direct proportion to the duration of the anesthetic, and the diminished alkali reserve continues for from one-half to one hour after the anesthetic. Prentice, Lund and Harbo [178] give the figures for alkali reserve as 0.23 before ether falling from 0.016 to 0.018 with ether. Raymond [179] finds that the fall in alkali reserve is relatively insignificant in acute shock, but with late shock the plasma may show a high alkali reserve. The condition of the animal cannot be judged by the alkali reserve. Adams and Sturges [180] find in fifty-four cases of effort syndrome that the carbon dioxid falls within normal limits, the combining power of the blood is normal and there is no indication that there is a decrease in the buffer salts of the blood.

The acid-base equilibrium of the blood is disturbed in acute tubular nephropathies. MacNider [181] thinks this shows the tubular part to be more important in the maintenance of acid base equilibrium than the vascular portion. With experimental infections Hirsch [182] finds that the blood alkali reserve is lowered at the time of the initial leukocytosis, then rises to, or above, the original level. In epidemic influenza and bronchopneumonia, Hachen and Isaacs [183] consider a comparison of the alkali reserve and the temperature as important in prognosis. With an alkali reserve of 46 or lower, the prognosis is good. With an alkali reserve of from 46 to 52, the prognosis is indefinite. With an alkali reserve of 53 and over, the prognosis is good. Sullivan and Stanton,[184] studying the alkali reserve in pellagra find little uncompensated acidosis. Henderson and Haggard [185] accelerate the elimination of carbon monoxid in carbon monoxid asphyxia by using a mixture of carbon dioxid and oxygen.

175. Buell, M. V.: J. Biol. Chem. **40**:29 (Nov.) 1919.

176. Tatum, A. L.: J. Biol. Chem. **41**:59 (Jan.) 1920.

177. Carter, W. S.: Arch. Int. Med. **26**:319 (Sept. 15) 1920.

178. Prentice, W.; Lund, H. O., and Harbo, H. G.: J. Biol. Chem. **44**:211 (Nov.) 1920.

179. Raymond, B.: Am. J. Physiol. **53**:109 (Aug.) 1920.

180. Adams, F. D.; Sturgis, D. C., and Sturges, C. C.: Am. J. M. Sc. **158**:816 (Dec.) 1919.

181. MacNider, W. de B.: Arch. Int. Med. **26**:1 (July) 1920.

182. Hirsch, E. F.: J. A. M. A. **75**:1204 (Oct. 30) 1920.

183. Hachen, D. S., and Isaacs, R.: J. A. M. A. **75**:1624 (Dec. 11) 1920.

184. Sullivan, M. X., and Stanton, R. E.: Arch. Int. Med. **26**:41 (July) 1920.

185. Henderson, Y., and Haggard, H. W.: J. Pharmacol. & Exper. Therap. **16**:11 (Aug.) 1920.

FERMENTS IN BLOOD

Lewis and Mason [186] find no constant relation between the variation in level of the blood ferments in nephritis and the progress of the disease. Fujimoto [187] thinks that diastatic substance passes from the pancreas to the liver where it is mixed with blood and lymph and its output is regulated by the liver. This is based on the fact that hepatotoxin decreases the diastase content of peripheral blood, while pancreatoxin and neurotoxin have no effect. Catalases, according to Reimann and Becker,[188] decrease in the blood in 65 per cent. of the cases during anesthesia. In anemia, Krumbhaar and Musser [189] find the catalase index (the catalase content divided by the hemoglobin content or the red blood cell count) of value in spite of wide individual variation. In anemias the catalase index varies from 15 to 53, with an average of 37+.

NITROGEN IN THE BLOOD

The study of nitrogen distribution in the blood of children results in the establishment of a better understanding of the normal. Utheim [190] finds that the serum protein in normal infants is from 6 to 6.5 per cent. until the tenth or eleventh month, when the protein begins to rise and reaches the adult level of about 8 per cent. by the fifteenth month. In athreptic and premature infants the protein may be as low as 4 per cent. Chapin and Meyers [191] report the findings on chemical examination of the blood of 149 children, including thirty-eight nephritics and six diabetics. They are similar to adults but the kidney of a child is more efficient, and nephritis does not result so quickly in urea retention as in adults. Stransky [192] examined the residual nitrogen in eighty-five children, including fifty infants. The high nitrogen content of the blood of the newborn has no clinical significance and diminishes by the end of the first week, after which the findings scarcely differ from those of early childhood. The values range from 40 to 50 mg. per 100 gm. of blood. Hammett [193] says that while total nitrogen, nonprotein nitrogen and sugar in the blood vary in the same person from week to week, the sum of the average deviation of the constituents for any given individual may be the *index of metabolic stability* for that person.

186. Lewis, D. S., and Mason, E. H.: J. Biol. Chem. **44**:455 (Nov.) 1920.
187. Fujimoto, B.: Am. J. Physiol. **50**:208 (Nov.) 1919.
188. Reimann, S. P., and Becker, C. E.: Am. J. Physiol. **50**:56 (Oct.) 1919.
189. Krumbhaar, E. B., and Musser, J. H.: J. A. M. A. **75**:104 (July 10) 1920.
190. Utheim, K.: Am. J. Dis. Child. **20**:366 (Nov.) 1920.
191. Chapin, H. D., and Meyers, V. C.: Am. J. Dis. Child. **18**:555 (Dec.) 1919.
192. Stransky: Monatschr. f. Kinderh. **19**:10 (Oct.) 1920.
193. Hammett, F. S.: J. Biol. Chem. **41**:599 (April) 1920.

Smith, Belt and Whipple [194] call attention to the remarkable stability of *serum protein concentration*.[195] When serum protein is depleted by interval bleeding and reinjection of washed corpuscles, there is an emergency reaction in fifteen minutes, then a gradual rise during the first twenty-four hours, and a more sluggish increase the next few days. The physiologic value of serum protein is not understood, but it may be a stabilizing value. With too great a dilution of serum proteins there is cell injury and clinical shock.[196]

Cullen and Van Slyke [197] partition the fibrin, globulin and albumin in the blood by means of nitrogen determinations. The fibrin nitrogen is determined directly, and globulin and albumin nitrogen are determined from the figures for total nitrogen, nonprotein nitrogen and fibrin nitrogen. In *glomerulonephritis and arteriosclerotic nephritis* Fitz [198] finds no relationship between the nonprotein nitrogen in the blood, the phenolsulphonephthalein test and the type of nephritis. Jacobson and Edwards [199] say the blood urea level is governed by previous diet, fluid retention, and unknown metabolic factors and is not a reliable index of nitrogen retention.

In anesthesia and after operations Reiman and Hartman [200] find blood urea and nonprotein nitrogen increased in all cases. Martin and Denis,[201] studying the chemical changes in the blood following roentgenray treatment of *leukemia* report that there is no connection between the white count and the uric acid concentration. In cases with a high nonprotein nitrogen there is a gradual fall, creatinin values are normal, urea is low, and uric acid is persistently high. Martin and Denis suggest that in leukemia there is a nitrogen compound in the white cells not accounted for in the present methods of microblood analysis.

In *pernicious anemia* and *severe anemias* Peters and Rubnitz [202] report that the nitrogen index $\frac{\text{per cent. whole blood nitrogen}}{\text{per cent plasma nitrogen}}$ is lowered and it may be used to indicate the state and progress of the anemic condition. Gettler and Lindeman [203] give figures for nonprotein nitrogen, urea nitrogen, amino-acid nitrogen, uric acid and creatinin in the blood obtained from thirty-two cases of *pernicious anemia*. Aminoacid

194. Smith, H. P.; Belt, E. A., and Whipple, G. H.: Am. J. Physiol. **57**: 54 (May) 1920.
195. Smith, H. P.; Belt, E. A., and Whipple, G. H.: Ibid. p. 72.
196. Smith, H. P.; Belt, E. A., and Whipple, G. H.: Ibid. p. 101.
197. Cullen, G. E., and Van Slyke, D. D.: J. Biol. Chem. **41**:587 (April) 1920.
198. Fitz, R.: Boston M. & S. J. **183**:247 (Aug. 26) 1920.
199. Jacobson, A. T. B., and Edwards, H.: Am. J. M. Sc. **159**:833 (June) 1920.
200. Reimann, S. P., and Hartman, F. L.: Am. J. Physiol. **50**:56 (Oct.) 1919.
201. Martin, C. L., and Denis, W.: Am. J. M. Sc. **160**:223 (Aug.) 1920.
202. Peters, A. W., and Rubnitz, A. S.: Arch. Int. Med. **26**:561 (Nov.) 1920.
203. Gettler, A. O., and Lindeman, E.: Arch. Int. Med. **26**:453 (Oct.) 1920.

nitrogen is always increased, and ninety per cent. of cases have increased uric acid, while the serum proteins may be reduced from 40 to 50 per cent.

In *influenzal pneumonia,* Wells [204] finds most fatal cases show an increase of blood uric acid, the average being 4.45 mg. per 100 c.c. of blood as contrasted with an average in the nonfatal cases of 3.14 mg. per 100 c.c. Pemberton and Foster [205] find a high blood creatinin in 50 per cent. of the cases of *arthritis* which in some cases declines with improvement. Dufour and Semelaigne,[206] in a case of *epileptiform seizures* after injections of neo-arsphenamin find an increase in the blood urea from 0.25 to 0.40 at normal times to 0.84 a few hours before a seizure. Loeper, Thinj and Tonnet [207] report profound alterations in the nitrogen equilibrium of the blood with residual nitrogen increased and urea nitrogen decreased in cancer patients. The frequent increase in blood urea without renal change is significant.

BLOOD SUGAR

Methods for the accurate estimation of blood sugar are still unsettled. The work of Cowie and Parsons [208] shows that the picrate solution used in the Lewis-Benedict method is sensitive to epinephrin in 0.025 mg. per cent., to acetone in blood solutions but not in water solutions, to diacetic acid and to creatinin. Creatinin does not often interfere. They suggest that the hyperglycemia occurring in emotional states may be due to epinephrin thrown into the circulation without mobilizing the glycogen stores in the liver. Rassero [209] finds both crystalloid and colloid elements in the serum from cattle, sheep, rabbits and guinea-pigs that produce vasoconstricting action on intestinal muscle, uterine muscle of cats and artery muscles in cattle. These substances resemble epinephrin. Lippmann [210] finds that the drop in the freezing point in diabetes does not parallel the intensity of the glycemia, and this indicates disturbance in the mechanism regulating the osmotic tension of the blood, and that other reducing substances beside glucose are present.

Feigl [211] modifies Bangs' micromethod for blood examination obtaining results with extracts from as small a quantity as 200 mg. of blood

204. Wells, C. W.: Arch. Int. Med. **26**:443 (Oct.) 1920.
205. Pemberton, R., and Foster, G. L.: Arch. Int. Med. **25**:243 (March) 1920.
206. Dufour, H. ,and Semelaigne, G.: Bull. et mém. Soc. méd. d. hôp. de Par. **44**:58 (Jan. 16) 1920.
207. Loeper, Thinj, and Tonnet: Progrès méd. **35**:159 (April 10) 1920.
208. Cowie, D. M., and Parsons, J. P.: Arch. Int. Med. **26**:333 (Sept.) 1920.
209. Rassero, J. R. F.: Nederlandsch Tijdschr. v. Geneesk. **1**:785 (March 6) 1920.
210. Lippmann, A.: Zentralbl. f. inn. Med. **41**:41 (Jan. 17) 1920.
211. Feigl, J.: Zentralbl. f. inn. Med. **41**:17 (Jan. 10) 1920.

and using picrate reduction for sugar. Silvestri and Aiello [212] object to Bangs' micromethod and offer a modification of Bertrand's method after adding a known amount of glucose to the solution. Wallis and Gallagher [213] give a new microchemical method for estimation of sugar in blood.

Mertz [214] analyzes the literature and decides that the carbohydrate metabolism of infants and young children obeys the same laws as adults. Strause [215] finds variations in the normal blood sugar due to weather conditions, all the curves in a group of individuals being higher in March than in September. Water intake and excretion do not affect blood sugar. Alimentary hyperglycemia reaches its height in normals in half an hour and descends at once, while in diabetes the height is reached, in one hour, and descends slowly. Brösamlen and Sterkel [216] find a marked reduction in blood sugar after physical exertion. Asphyxial blood transfused into rabbits, in Yamakami's [217] experiments causes a rise in the blood sugar content, which is not due to the sugar in the asphyxial blood injected. Delatour [218] thinks that the pancreas produces substances that favor metabolism of sugar which explains the hyperglycemia in depancreatized dogs. Ross and Davis [219] conclude that the hyperglycemia with ether is due to reduction of the influence of the internal secretion of the pancreas. Rhodenburg and Pohlman [220] think that the hyperglycemia following injection of fats and polypeptids which are supposed not to produce antibody production, is protective and may be a test to check antibody production when neither precipitin, agglutinins or lysins can be demonstrated. Friedenwald and Grove [221] find that carcinomia of the gastrointestinal tract gives a characteristic blood sugar tolerance curve, whether cachexia exists or not.

BLOOD LIPOIDS

Burns [222] thinks that the origin of xanthoma multiplex is an increase in the blood cholesterin with deposits of cholesterin in the skin.

Schippers [223] questions whether the low fat content of the blood (about half the normal content) in infants with exudative diathesis

212. Silvestri, S., and Aiello, G.: Policlinico, Rome 27:643 (June 21) 1920.
213. Wallis, R. L. M., and Gallagher, C. D.: Lancet 2:784 (Oct. 16) 1920.
214. Mertz, A.: Arch. f. Kinderh. 68:254 (Oct. 16) 1920.
215. Strause, S.: Arch. Int. Med. 26:751 (Dec.) 1920.
216. Brösamlen, O., and Sterkel, H.: Deutsch. Arch. f. klin. Med. 130:358 (Oct. 24) 1919.
217. Yamakami, K.: Am. J. Physiol. 50:177 (Nov.) 1919.
218. Delatour, B. J.: Arch. Int. Med. 25:1542 (April) 1920.
219. Ross, E. L., and Davis, L. H.: Am. J. Physiol. 53:391 (Oct.) 1920.
220. Rhodenburg, G. L., and Pohlman, H. E.: Am. J. M. Sc. 159:853 (June) 1920.
221. Friedenwald, J., and Grove, G. H.: Am. J. M. Sc. 160:313 (Sept.) 1920.
222. Burns, F. S.: Arch. Dermat. and Syph. 2:415 (Oct.) 1920.
223. Schippers, J. C.: Nederlandsch Tijdschr. v. Geneesk. 2:1081 (Sept. 18) 1920; Abstr. J. A. M. A. 75:1530 (Nov. 27) 1920.

may not throw light on the nature of the anomaly. Strathmann-Herwig [224] finds that breastfed and artificially fed infants who are normal have the same cholesterin content in the blood serum. Cholesterin is usually increased in infections and decreased in anemia and infantile scurvy. Richter-Quittner [225] says that normally cholesterin is divided about equally between the blood plasma and the corpuscles. Free cholesterin occurs only in the corpuscles, and cholesterin esters in the plasma, but with disease processes, free cholesterin may occur in the plasma also together with the cholesterin esters. Chaffard, Laroche and Grigaut [226] report a marked drop in cholesterin in the blood during the febrile states, with a high rise after defervescence in moderate cases, but no rise in mild or severe cases. Cholesterin probably has an antitoxic action and presides over the antibody formation. Hypercholesterinemia occurs in chronic nephritis and may be a differential diagnostic point ruling out cardiac edema. Henes [227] finds hypercholesterinemia usually in cases of chronic nephritis that are progressing favorably. He also assigns a protective rôle to cholesterol. Blood lipoids play a part analogous to antitoxin. They seem to act as a protection and to counteract certain poisonous substances. Beumer [228] notes that the hypercholesterinemia in nephroses is independent of edema and fever and could not be influenced by restriction of fat or lipoid in the diet.

Kipp [229] finds that transfusion of whole blood does not alter the cholesterol content in the blood in cases of pernicious anemia, and in pneumonia he finds a primary hypocholesterinemia dependent in degree on the activity of the leukocytes, a secondary hypercholesterinemia and the return to normal.[230] The variations are dependent on the leukocytes, and the lipoids act as an antitoxic substance.

<center>HYPERINDICANEMIA</center>

Van Vloten [231] tabulates the indican and the urea content of the blood serum from forty patients showing the variations with diet and the importance of blood indican for prognosis. The normal range limits by different observers run from 1.4 to 1.8 mg. per liter. In uremia,

---

224. Strathmann-Herwig: Monatschr. f. Kinderh. **19**:20 (Oct.) 1920.

225. Richter-Quittner, M.: Arch. f. inn. Med. **1**:425 (June 1) 1920.

226. Chaffard, A.; Laroche, G., and Grigaut, A.: Ann. de Méd. **8**:69 (Aug.) 1920.

227. Henes, E.: Arch. Int. Med. **25**:411 (April) 1920.

228. Beumer, H.: Arch. f. Kinderh. **68**:64 (Aug. 31) 1920.

229. Kipp, H. A.: J. Biol. Chem. **43**:383 (Sept.) 1920.

230. Kipp, H. A.: J. Biol. Chem. **44**:215 (Nov.) 1920.

231. Van Vloten, W. J. Van B.: Nederlandsch Tijdschr. v. Geneesk. **2**:585 (Aug. 14) 1920; Abstr. J. A. M. A. **75**:1170 (Oct. 23) 1920.

the urea and the indican content do not run parallel, although there is usually indicanemia; when it is persistently high, even though the urea content is normal, the prognosis is grave.

INORGANIC CONSTITUENTS IN BLOOD

Scheer [232] finds that the *chlorid level in the blood* serum of infants is dependent on the secretion of gastric juice. During digestion the chlorin level declines; to rise after the stomach is emptied. Host,[233] using Bangs' micromethod, finds that the chlorids exist chiefly in the serum and less in the corpuscles. Fredericia [234] confirms Van Slyke's work on the partition of chlorids between the plasma and the corpuscles. Rodillon,[235] and Meyers and Short [236] give new modifications or methods for determining the chlorids in blood. Rodillon calls the chlorids in the blood the index of kidney condition.

Denis and Minot [237] study the *phosphate retention in the blood in nephritis.* In 65 per cent. of the nephritis cases there was definite retention of inorganic phosphates in the plasma. In eleven fatal cases there was a premortal rise to as much as ten times the normal value.

The *calcium content of the blood* is still a matter of great interest. An editorial [238] in the *Journal of the American Medical Association* summarizes the uses of calcium in bones, in the clotting of blood and milk, in the maintenance of physiologic equilibrium, in the preservation of normal vessel permeability, and in the normal irritability of parts of the nervous system. Stheeman and Arntzenius [239] consider the "calcipriva stigma" the basis for spasmophilia, habitus asthenicus and universal asthenia. In fifty-eight healthy children the calcium content of the blood was constantly between 12 and 13 mg. per 100 c.c. of serum; in six children the range was from 8.25 to 17 mg. per 100 c.c. of serum.[240] The figures are low in prerachitic conditions, intestinal infantilism, tuberculosis and asthenia, the severity of the condition being reflected in the decrease in calcum. Erb's sign is nearly always positive with a low calcium content, becoming more and more positive as the calcium deficit becomes greater. Chvostek's sign has the same significance. In rachitis the calcium content in the blood may be high, but the

232. Scheer, K.: Jahrb. f. Kinderh. **91**:347, 1920.
233. Host, H. F.: J. Lab. & Clin. M. **5**:713 (Aug.) 1920.
234. Fredericia, L. S.: J. Biol. Chem. **42**:245 (June) 1920.
235. Rodillon: Presse méd. **28**:85 (Jan. 31) 1920.
236. Meyers, V. C., and Short, J. J.: J. Biol. Chem. **44**:47 (Oct.) 1920.
237. Denis, W., and Minot, A. S.: Arch. Int. Med. **26**:99 (July) 1920.
238. Editorial, J. A. M. A. **75**:941 (Oct. 2) 1920.
239. Stheeman, H. A., and Arntzenius, A. K. W.: Nederlandsch Tijdschr. v. Geneesk. **1**:1030 (March 27) 1920.
240. Stheeman, H. A., and Arntzenius, A. K. W.: Nederlandsch Tijdschr. v Geneesk. **1**:1168 (April 3) 1920.

calcium in the tissues is actually deficient. It is evident from the positive Erb's sign that there is more than one kind of calcium in the blood, one efficient for growth and one nonefficient. The calcium content of the serum is important, but the calcium balance does not tell whether there is calcium impoverishment or calcium abundance until combined with nerve signs. Handowsky [241] is unable to find any difference in the calcium range in adults with a positive Chvostek sign and adults without a positive Chvostek. Jacobowitz [242] finds children free from tetany have a higher calcium level in the blood than children with tetany.

Kramer and Howland [243] show that the calcium in the blood serum as determined by their method is remarkably constant in adults, the normal content being from 9 to 10 mg. per 100 c.c. of serum. The decrease in tetany may be more than 50 per cent.

Denis and Minot,[244] and Clark [245] substantiate the findings that calcium by mouth, or intravenously or subcutaneously and the feeding of diets rich in calcium does not make any appreciable difference in the calcium content of bones, blood and other tissues. Stheeman and Arntzenius [239] point out that cod liver oil and phosphorus promote the retention of calcium in the body. Krehbiel [246] finds that the blood calcium is within normal limits in cancer and obliterating arteritis, showing that calcium metabolism is not a factor in cancer.

TESTS FOR OCCULT BLOOD

Penn [247] makes a smear of feces on a microscope slide, spreads two or three drops of glacial acetic acid over the smear, and heats gently over a flame. On the addition of one or two drops of benzidin dissolved in alcohol and the same amount of hydrogen peroxid, a dark blue color develops almost immediately if blood be present. The method commends itself as rapid and simple. Boas [248] says the reagents are often too strong in the benzidin test. He used 0.5 per cent. benzidin solution and in place of hydrogen peroxid he used barium dioxid which is more stable. With the test used in this way very slight hemorrhages may be missed.

RED BLOOD CORPUSCLES

The *hemoglobin content* shows a diurnal variation which commonly reaches 10 per cent. but may reach 30 per cent. (Dreyer, Bazett and

241. Handowsky, I.: Jahrb. f. Kinderh. **91**:432, 1920.
242. Jocobowitz, S.: Jahrb. f. Kinderh. **92**:256, 1920.
243. Kramer, B., and Howland, J.: J. Biol. Chem. **43**:35 (Aug.) 1920.
244. Denis, W., and Minot, A. S.: J. Biol. Chem. **41**:357 (March) 1920.
245. Clark, G. W.: J. Biol. Chem. **43**:89 (Aug.) 1920.
246. Krehbiel, O.: J. Cancer Res. **5**:199 (April) 1920.
247. Penn, S.: Med. J. Australia **1**:525 (June 5) 1920.
248. Boas, I.: Berl. klin. Wchnschr. **56**:939 (Oct. 6) 1919.

Pierce,[249]) the excursions being more marked with a low hemoglobin content. McEllroy [250] uses the fact that potassium ferricyanid does not liberate oxygen from methemoglobin but does from hemoglobin to determine the amount of methemoglobin. Total hemoglobin is determined, then the oxygen capacity and the difference gives the methemoglobin. Hemoglobin in itself has been held to be toxic, but Bayliss [251] finds that hemolysis in itself does not cause injury, hemoglobin is harmless when circulating free in plasma, and can carry oxygen. The results of the transfusion of incompatable blood are probably due to the action of a foreign protein.

To study the blood of animals in vitro, Normet [252] injects sodium citrate into the circulation. He demonstrates to his own satisfaction the development of blood corpuscles, eosinophils and erythrocytes, direct from the mononuclear leukocytes by a process of budding which is a method of cell reproduction not suspected in metazoa. Rieux [253] gives the "genealogic tree of the blood corpuscle" showing additional stages preceding the mature erythrocytes and polymorphonuclears. The presence of the normomegaloblastic reaction, of nuclear relics and basophil granular erythrocytes are signs of recuperation of blood forming elements, and signs that the bone marrow is capable of producing blood corpuscles. Bockhoven [254] thinks that basophil inclusions in the erythrocytes must be nuclear remnants and are signs of grave import. Walterhöfer [255] says their pathologic significance lies not in the inclusion bodies in the erythrocytes but in the fact that red cells with azurophil inclusion bodies appear in the peripheral circulation. They are new cells, traceable to some bone marrow reaction. Cunningham [256] suggests that the reticulated net work in the red blood cells may give a clue to the age of the cell, those with reticulation being immature and being an index to the hematopoietic activity. To stain the reticulum, smear a small drop of a 0 5 per cent. solution of brilliant cresyl blue over a small area on the slide, let dry, then wipe off the thick margin. Take a fresh blood drop on a cover slip, drop face down over the area of stain, make a smear and dry. Stain with Wright's stain. The reticulum is deep or light blue. Bauer and Buschner [257] testing the "resistance

249. Dreyer, G.; Bazett, H. C., and Pierce, H. F.: Lancet **2**:588 (Sept. 18) 1920.

250. McEllroy, W. S.: J. Biol. Chem. **42**:297 (June) 1920.

251. Bayliss, W. M.: Brit. J. Exper. Path. **1**:1 (Feb.) 1920.

252. Normet: Bull. de l'Acad. de méd. Par. **83**:163 (Feb. 24) 1920; Abstr. J. A. M. A. **74**:1489 (May 22) 1920.

253. Rieux, J.: Arch. d. mal. du cœur **13**:254 (June) 1920.

254. Bockhoven, M.: Ztschr. f. klin. Med. **89**:304, 1920.

255. Walterhöfer, G.: Deutsch. med. Wchnschr. **46**:116 (Jan. 29) 1920.

256. Cunningham, T. D.: Arch. Int. Med. **26**:405 (Oct.) 1920.

257. Bauer, J., and Buschner: Deutsch. Arch. f. klin. Med. **130**:172 (Sept. 26) 1919.

range" of erythrocytes to varying concentration of salt solution find the widest range in severe anemias, and the smallest range in mild tuberculosis. The range varies in the same person at different times, and the younger erythrocytes have the highest resistance.

Craik [258] uses doses of lead by mouth to produce polychromatic and punctated red corpuscles. These marked discs in the circulation are young corpuscles, and they are means of tracing malarial parasites. Multiple infections of the marked discs suggest that the youngest corpuscles are the least resistant to the plasmodium.

Wyss [259] presents evidence that in the blood circulation erythrocytes are round or egg shaped, but that they collapse with the escape of the oxygen when the blood is drawn. Taylor [260] finds that most of the red blood corpuscles injected subcutaneously do not reach the circulation as cells, although the hemoglobin is raised by such an injection.

Kambe and Komiya [261] conclude that preserved erythrocytes may retain their physiologic properties and live a normal length of life after transfusion. In transfusion after hemorrhage, nucleated forms may be absent so that the newly supplied cells prevent stimulation of the blood forming organs. In a blood effusion in a cadaver exhumed seven months after death, Straussmann [262] finds the red blood corpuscles unchanged, and well preserved, the lymphocytes present but altered, and the polymorphonuclears gone completely.

The sedimentation or sinking velocity of blood corpuscles in paresis is increased to about one-sixth of the time required in dementia praecox. Plant [263] says that acceleration of sedimentation is a pathologic sign whose significance has not been determined, but the acceleration in pregnancy may have a diagnostic value. Linzenmeier [264] finds that the sedimentation time for corpuscles in the blood of nonpregnant women is five or six hours, while in pregnant women from the fourth month on, the time is less than two hours, decreasing to fifty minutes in the last three months.

Goodman [265] finds an increase in red blood cells following inflation of the peritoneal cavity with oxygen; that this may be due to the mechanical effect of pressure on venous trunks is shown by the fact that the same effect can be produced in rabbits by nitrogen inflation.

258. Craik, R.: Lancet **1**:1110 (May 22) 1920.
259. Wyss, O.: Schweiz. med. Wchnschr. **50**:226 (March 18) 1920.
260. Taylor, R.: Am. J. Dis. Child. **20**:337 (Oct.) 1920.
261. Kambe, H., and Komiya, E.: Am. J. Physiol. **53**:1 (Aug.) 1920.
262. Straussmann, G.: Berl. klin. Wchnschr. **56**:994 (Oct. 20) 1919.
263. Plant, F.: München. med. Wchnschr., March 5, 1920, p. 279.
264. Linzenmeier, G.: Zentralbl. f. Gynäk. **44**:816 (July 24) 1920.
265. Goodman, C.: J. A. M. A. **74**:1515 (May 29) 1920.

Gregg, Lutz and Schneider [266] contrast the theories of blood concentration versus a dormant supply of erythrocytes as the cause of fluctuations in the distribution of hemoglobin and erythrocytes under states of low oxygen tension. The question seems to have been settled in a satisfactory manner by records taken on the summit of Pike's Peak and at Cripple Creek during the summer of 1903 when comparisons between the curves of the red corpuscle increase, the hemoglobin and the specific gravity from daily records on six normal healthy individuals, show that the increase and daily fluctuation cannot be accounted for by different degrees in blood concentration (Kemp[267]) and must be due to a storage of mobile red corpuscles.

POLYCYTHEMIA

Thaysen [268] makes systematic red counts over a long period of time in polycythemia. There are remarkable fluctuations of as much as 5,000,000 in a period of twenty-four hours. This is explained by varying contraction and dilation of skin capillaries due to an unstable vasomotor system. An editorial [269] in the *Journal of the American Medical Association* states that the real factor in polycythemia is unknown, that splenic tuberculosis as a cause has been abandoned. There are two accepted causes, for true polycythemia, one hyperplasia of the erythroblastic bone marrow, and the other a decrease in the rate of destruction of the red corpuscles. Lamson [270] says that *acute polycythemia* is always due to blood concentration, no matter whether it be physiologic, as the polycythemia in emotional states, or produced by local irritation or the injection of histamin. Bing [271] reports four cases of polycythemia with duodenal ulcer. The polycythemia here may be due to abnormal loss of sodium chlorid.

Weber[272] classifies the *secondary forms of polycythemia rubra* as: (1) Polycythemia hypertonica; no splenomegaly; blood pressure, 180 mm.; (2) splenomegalic polycythemia rubra, with tuberculosis or other splenic disease; (3) secondary polycythemia rubra, with splenomegaly and portal stasis, and (4) chronic cardiopulmonary cyanosis or Ayerza's disease.

266. Gregg, H. W.; Lutz, B. R., and Schneider, E. C.: Am. J. Physiol. **50:** 216 (Nov.) 1919.

267. Kemp, G. T.: Am. J. Physiol. **10:**33, 1903-1904.

268. Thaysen, T. E. H.: Ugesk. f. Læger **82:**473 and 514 (April 8 and 15) 1920.

269. Editorial, J. A. M. A. **74:**1781 (June 26) 1920.

270. Lamson, P. D.: J. Pharmacol. & Exper. Therap. **16:**125 (Sept.) 1920.

271. Bing, H. I.: Ugesk. f. Læger **82:**337 (March 11) 1920.

272. Weber, F. P.: Brit. M. J. **2:**658 (Oct. 30) 1920.

True polycythemia rubra in Herrenheiser's [273] case was an instance of increased production of red cells and reduced rate of destruction. Böttner [274] recommends irradiation of the long and short bones controlled by the blood picture. The roentgen-ray therapy of the spleen should be limited to irritative doses.

ANEMIAS

The question of the value of *iron in the treatment of anemias* is still under controversy. Nageli [275] thinks that in proper dosage iron elicits a strong bone marrow reaction throwing quantities of young red cells into the blood stream. Alder [276] says the improvement with Blaud's pills reaches its acme in three weeks, and then remains stationary. Hooper, Robscheit and Whipple [277] show that Blaud's pills have no influence in simple secondary anemias even when combined with varied diets.[278] Of the diets of value in secondary anemia, cooked lean beef heart and cooked liver are important for blood regeneration in dogs. Water extracts of meat and liver are not so effective.[279] Bread and milk diet does not give complete regeneration after hemorrhage, while the increase in red blood cells and hemoglobin is greater in a fasting animal than in one fed on sugar.[280]

Larrabee [281] considers *aplastic anemia* a type of an anemia group. Most benign anemias are due to an increased destruction or loss of blood ce'ls, to compensate which some of the yellow bone marrow changes to red marrow, produces new corpuscles and then returns to the normal adult condition. In pernicious anemia there is intense marrow hyperplasia which still is not sufficient to balance the destruction. In aplastic anemia the marrow does not produce even the normal amount of blood cells and there is no compensatory hyperplasia. In aplastic anemia the power to produce red corpuscles, myelocytic leukocytes and platelets is all involved. The platelet decrease and prothrombin decrease explains the tendency to hemorrhage. Purpura hemorrhagica is probably an incomplete form of aplastic anemia, only the platelet producing power being affected. Mensi [282] adds to the cases of

273. Herrnheiser, G.: Deutsch. Arch. f. klin. Med. **130**:315 (Oct. 24) 1920.
274. Böttner, A.: Deutsch. med. Wchnschr. **46**:66 (Jan. 15) 1920.
275. Nägeli: Schweiz. med. Wchnschr. **50**:661 (July 29) 1920; Abstr. J. A. M. A. **75**:966 (Oct. 2) 1920.
276. Alder, A.: Ibid., p. 663.
277. Hooper, C. W.; Robscheit, F. S., and Whipple, G. H.: Am. J. Physiol. **53**:263 (Sept.) 1920.
278. Whipple, G. H.; Hooper, C. W., and Robscheit, F. S.: Am. J. Physiol. **53**:151 (Sept.) 1920
279. Hooper. C. W.; Robscheit, F. S., and Whipple, G. H.: Ibid., p. 206.
280. Whipple, G. H.; Robscheit, F. S., and Hooper, C. W.: Ibid., p. 286.
281. Larrabee, R. C.: J. A. M. A. **75**:1630 (Dec. 11) 1920.
282. Mensi, E.: Pediatria, Naples **28**:785 (Sept.) 1920.

pernicious anemia in children reported in the literature, making a total of twenty-nine cases. The etiology is obscure after the elimination of a few cases due to syphilis, tuberculosis and intestinal parasites. Meulengracht [283] reports *familial pernicious anemia* developing in four sons and the son of one daughter. This familial occurrence confirms the assumption of one or more endogenous factors.

Kaznelson [284] cites a case of *hemolytic anemia* dating from childhood, in which splenectomy ended the symptoms but did not eradicate the disease. Fraginoli [285] studied nine cases of hemolytic jaundice. The characteristic feature is the presence of numerous nucleated red corpuscles, megaloblasts, without sufficient anemia to account for them. This, he considers, is due to the persistence of megaloblast-producing tissue which normally undergoes involution soon after birth. The persistence of this one element throws the whole system out of gear. Clark and Evans [286] suggest that the reason why hemolysis does not occur in normal blood is because the serum has a protective power against the natural hemolysins in the blood. If this protective power be diminished the normal hemolytic substances may act without any increase in the hemolysin or the introduction of foreign hemolysins. Ordinarily, the protective power is a constant, but in the anemias, especially with splenic involvement, the protective power is diminished.

Hallez [287] reports two cases of anemia with splenomegaly in infants. Tuohy's [288] case was associated with a leukocytosis of 65,000, 99 per cent. of the leukocytes being polymorphonuclears. In embryos up to the fourth month both spleen and bone produce red blood cells. After the fourth month, erythrocytes and myeloblasts are formed almost entirely from bone marrow and the spleen functions in blood destruction, the two hyperfunctioning coordinately. The method of leukocyte destruction and replacement is not known.

In hemolytic anemias, Speidel, Hoff and Nickson [289] suggest partial splenectomy. In dogs partial splenectomy is accompanied by distinct polycythemia. Biffis,[290] Losio [291] and Hartmann [292] report cases in

283. Meulengracht, E.: Ugesk. f. Læger **82**:777 (June 17) 1920; Abstr. J. A. M. A. **75**:644 (Aug. 28) 1920.

284. Kaznelson, P.: Wien. Arch. f. inn. Med. **1**:563 (Aug.) 1920.

285. Fraginoli, A.: Policlinico, Rome **27**:337 (Sept.) 1920.

286. Clark, H. M., and Evans, F. A.: Bull. Johns Hopkins Hosp. **31**:354 (Oct.) 1920.

287. Hallez, G. L.: Nourrisson, Paris **8**:154 (May) 1920.

288. Tuohy, E. L.: Am. J. M. Sc. **60**:18 (July) 1920.

289. Speidel, W. C.; Hoff, E., and Nickson, D. H.: Northwest Med. **19**:94 (April) 1920.

290. Biffis, P.: Policlinico **26**:393 (Nov.) 1919.

291. Losio, L.: Ibid., p. 410.

292. Hartmann, H.: Bull. de l'Acad. de méd. Par. **83**:599 (June 29) 1920; Abstr. J. A. M. A. **75**:571 (Aug. 21) 1920.

which the spleen was removed. Cushing and MacCallum [293] report two cases of splenic anemia with splenectomy in 1898. So little has been added to our knowledge of the pathology of the spleen that MacCallum's report in 1898 is included unchanged. The blood changes after removal of the spleen in a case without anemia, were studied by Hall.[294] The leukocyte count was increased for three months with no eosinophilia. The Arneth index suggests that the increase is due, in part, to the removal of some factor restricting the production of white corpuscles. Henn [295] finds in experimental animals that the corpuscles of splenectomized dogs are more strongly resistant to hypotonic sodium chlorid solutions than in control animals; and in young animals the coagulation time is hastened. Downs and Eddy [296] find that the subcutaneous injection of free splenic extract is followed immediately by a temporary decrease in the number of the red blood cells.

Sappington [297] reports another case of Gaucher's disease bringing the total of authentic cases with histologic examinations to twenty-five cases.

THE LEUKOCYTES

Loeper [298] studied the leukocytosis in animals after the injection of epinephrin. The mononuclear leukocytes seem to share in the production of antibodies, and increasing numbers presage recovery and immunity. Sprunt and Evans [299] report six cases of acute tonsillitis, infections of the upper respiratory tract and moderate general lymphadenitis in which there was a mononuclear leukocytosis. Audain [300] says that invading infections are combated by polymorphonuclear leukocytes when the region invaded is poor in lymphoid elements; but when lymphoid elements are present, they assume the local defense and mononucleosis is the rule. With infections of the lungs and bladder there is a polynucleosis throughout. Infections of the intestine, glands and spleen show a mononucleosis. If the lymphoid elements are not equal to the task, it is begun by the polymorphonuclears until the mononuclears become adequate for the defense. Ruppanner [301] finds that persons coming to the mountains have a pronounced leukocytosis at first, an acclimation leukocytosis, which yields in about six weeks to the moun-

293. Cushing, H., and MacCallum, W. G.: Arch. of Surg. **1**:1 (July) 1920.
294. Hall, M. W.: Am. J. M. Sc. **160**:72 (July) 1920.
295. Henn, C. S.: Am. J. Physiol. **52**:562 (July) 1920.
296. Downs, A. W., and Eddy, N. B.: Am. J. Physiol. **51**:279 (March) 1920.
297. Sappington, S. W.: J. A. M. A. **75**:105 (July 10) 1920.
298. Loeper, M.: Progrès méd. **35**:37 (Jan. 25) 1920.
299. Sprunt, T. P., and Evans, F. A.: Bull. Johns Hopkins Hosp. **31**:410 (Nov.) 1920.
300. Audain, L.: Presse méd. **28**:796 (Nov. 6) 1920.
301. Ruppanner, E.: Schweiz. med. Wchnschr. **50**:105 (Feb. 5) 1920.

tain leukocyte picture, i.e. a total count at the low range of normal, with the percentage of lymphocytes above normal and the neutrophil percentage below normal.

Otani[302] finds an increased phagocytic power for the particular species of invading organisms. The acceleration may be an immunologic reaction, making an early diagnosis of tuberculosis, typhoid and dysentery possible. Tunnicliff[303] finds that injections of leukocyte extracts produce an increase in the number and in the activity of the leukocytes.

Schilling[304] thinks the number of nuclear lobes in the neutrophil polymorphonuclears is as important as the pulse in examinations of the heart. Displacement to the left in the Arneth classification is a constant clinical symptom in some infections. Friedburg[305] gets no effect on the white blood corpuscles by stimulation of the vegetative nervous system in children. There is no vagotonic or sympatheticotonic blood picture. The eosinophils have a tendency to parallel the lymphocyte variations, and the mononuclears parallel the polymorphonuclears.

Giffin[306] reports a persistent eosinophilia of 73.6 per cent. in a case with a leukocytosis of 21,800 and splenomegaly. Removal of the spleen increased the eosinophils to 90.7 per cent. and the leukocytes to 211,000. A special function of the spleen with respect to eosinophil cells or with respect to the toxins the eosinophils absorb is suggested. Klinkert[307] considers eosinophilia a sign of a constitutionally inferior autonomic nervous system entailing a predisposition to asthma, gout, urticaria and migraine.

Pepper[308] diagnosed a case of typhoid fever on the finding of numerous cells resembling endothelial leukocytes in the urine. Tryon[309] gives the leukocyte reactions in paratyphoid dysentery and after vaccination. The differential counts are not so variable as the total counts, and in all cases the platelet count was high. Ingles[310] finds a definite but variable *leukocytosis in trench fever*. Both polymorphonuclears and nongranular cells are increased, the nongranular cells being the more numerous which may be a factor in differential diagnosis of trench fever.

302. Otani, M.: Med. Rec. **97**:439 (March 13) 1920.
303. Tunnicliff, R.: J. Infect. Dis. **26**:447 (May) 1920.
304. Schilling, V.: Ztschr. f. klin. Med. **89**:1, 1920.
305. Friedburg, E.: Monatschr. f. Kinderh. **18**:432 (Aug.) 1920.
306. Giffin, H. Z.: Am. J. M. Sc. **158**:618 (Nov.) 1919.
307. Klinkert, D.: Ztschr. f. klin. Med. **89**:143, 1920.
308. Pepper, O. H. P.: Am. J. M. Sc. **160**:336 (Sept.) 1920.
309. Tryon, G.: Boston M. & S. J. **183**:643 (Dec.) 1920.
310. Ingles, W. K.: Med. J. Australia **2**:431 and 454, 1919.

Canelli [311] calls attention to the fact that azurophilia is not a blood finding that is specific for measles, being also found in pneumonia and scarlet fever; but the *azurophilia in measles* is so marked and pronounced that it may aid in differential diagnosis.

Schilling [312] reports two cases of ulcerative endocarditis giving very high mononuclear leukocyte counts. Rosenow [313] considers the leukopenia of influenza due to the peculiar properties of the streptococci or other organisms associated with the disease.

Escomel [314] examines blood for bacteria before any surgical operations. The blood is mixed with 15 c.c. of a 1 per cent. acetic acid solution, centrifuged and the supernatent fluid poured off. The sediment is washed with physiologic serum, and stained smears made from the sediment show leukocytes, bacteria and parasites.

LEUKEMIA

Decastello [315] calls attention to the occurrence of *Bence-Jones proteinuria* in leukemia. It seems to originate in a pathologic condition of the bone marrow. Howell [316] finds that six of eight patients with leukemia produced no agglutinins after injection of typhoid vaccine. This suggests that in leukemia the power to produce anticellular antibodies also resides in the hematopoietic tissue.

Tancre [317] reports a case of acute lymphatic leukemia developing after a suppurating process at the umbilicus. Ward [318] considers the preleukemic states in infancy, referring to the large series of cases of Von Jaksch's disease reported by Martelli.[319] The blood may show a myeloid blood picture with slight leukocyte increase, a few myelocytes and anomalous cells, Tuerck cells, plasma cells and large mononuclears, and perhaps a few nucleated red cells, and a color index of over one. Gunewardene [320] followed the development of such a case through to a definite myelogenous leukemia picture.

Fitz [321] reports the simultaneous occurrence of diabetes and myelogenous leukemia in one patient, which he believes are independent of each other. Ravenna [322] cites three cases of *myelogenous leukemia*

311. Canelli, A. F.: Rev. di clin. Pediatrica **18**:82 (Feb.) 1920.
312. Schilling, V.: Ztschr. f. klin. Med. **88**: 1919.
313. Rosenow, E. C.: J. Infect. Dis. **26**:492 (June) 1920.
314. Escomel, E.: Anales de la Faculdad de med. de Lima **3**:12 (July-Aug.) 1920; Abstr. J. A. M. A. **75**:1601 (Dec. 4) 1920.
315. Decastello, A.: Wien. Arch. f. inn. Med. **1**:335 (June 1) 1920.
316. Howell, K. M.: Arch. Int. Med. **26**:706 (Dec.) 1920.
317. Tancré, E.: Arch. f. Kinderh. **67**:7 (Nov. 30) 1918.
318. Ward, G.: Brit. J. Child. Dis. **17**:18 (Jan.-March) 1920.
319. Martelli, C.: Gazz. Internaz. di Med., 1919. Quoted from Ward.
320. Gunewardene, T. H.: Brit. J. Child. Dis. **17**:9 (Jan.-March) 1920.
321. Fitz, R.: J. A. M. A. **75**:1331 (Nov. 13) 1920.
322. Ravenna, F.: Riforma med. **36**:86 (Jan. 24) 1920.

systematically treated with benzol. The effect is purely symptomatic and the symptoms return in a more grave form. Lafleur's [323] patient improved under the combination of benzene and Roentgen-ray treatment.

THE BLOOD PLATELETS

Marchesini [324] thinks platelets result from the debris of unstable red corpuscles. The process of platelet formation may be watched in the large erythrocytes of frogs and birds. Mallory and Medlar [325] find interesting changes in blood plates under the dark field microscope. At first, the platelets are round or ovoid, then they elongate into threads and star-shaped bodies with threadlike projections showing serpentine movement. In stained preparations these platelets give the reaction of fibrin.

Gram [326] uses the Thomsen method of obtaining a hemogeneous suspension of platelets in plasma, and then dilutes 1:20 with a 2 per cent. solution of liquor formaldehyd in 0.9 per cent. sodium chlorid solution and counts direct in a Thoma Zeiss chamber.[327] This gives the number of platelets per c. mm. of citrated plasma. This figure is multiplied by constants which are determined by the hemoglobin content to find the number of plates in whole blood. The normal count is between 300,000 and 450,000. Pernicious anemia with a platelet count of under 100,000 tends to terminate fatally without remissions. Jost [328] finds that platelet extract by the mouth shortens the coagulation time and tends to arrest hemorrhage.

THE COAGULATION OF THE BLOOD

Several new methods for determining the coagulation time of blood are given. Gram [329] finds that too low recalcinations of citrated plasma lengthen the coagulation time. He uses the sedimentation plasma from the Thomsen method for counting blood plates because in the centrifugalized specimen the blood platelets are thrown down with the reds, and the coagulation time is doubled in normal bloods but not in bloods where the platelets are deficient. In hemophilia, the coagulation time is lengthened with a normal platelet count. This may be used for the diagnosis of the hemorrhagic diathesis. Love [330] determines the coagu-

323. Lafleur, H. A.: Canad. M. A. J. **10**:996 (Nov.) 1920.
324. Marchesini, R.: Policlinico **27**:227 (Feb. 23) 1920.
325. Mallory, F. B., and Medlar, E. M.: J. M. Res. **41**:327, 1920.
326. Gram, H. C.: Arch. Int. Med. **25**:325 (March) 1920.
327. Gram, H. C.: Ugesk. f. Læger **82**:718 (June 3) 1920; Abstr. J. A. M. A. **75**:282 (July 24) 1920.
328. Jost, W.: Cor.-Bl. f. schweiz. Aerzte **49**:1909 (Dec. 11) 1919.
329. Gram. H. C.: Bull. Johns Hopkins Hosp. **31**:364 (Oct.) 1920.
330. Love. G. R.: Med. Rec. **98**:436 (Sept.) 1920.

lation time by means of capillary tubes. The blood is drawn into paraffined test tubes and within two minutes is sucked up in capillary tubes and the time taken. Two minutes before the normal coagulation time, 2 cm. of the first tube is broken off drawing the fragments gently apart to avoid injuring the fibrin thread. Other segments of tube are broken off until the time interval is such that the fibrin thread will stretch from 7 to 10 mm. across the break. This is the end point. Rodda [331] uses a drop method, the drops from the heel of the baby being received in a clean watch glass containing a No. 6 shot. A second watch glass is inverted over the first. The crystal is tilted every thirty seconds, until the shot no longer rolls. The average clotting time for a new-born baby is seven minutes with a range of from five and one-half to eight and one-half minutes. King and Murray [332] draw the blood into open tubes with attachment below for a stop cock and a Luer needle. Two c.c. are drawn into the tube direct from the vein and kept at a temperature of from 65 to 90 F. The coagulation time is the nearest half minute from the instant the blood first appears to the moment when the tube may be inverted without displacing the clot.

The *coagulation time* in embryonic blood of the pig, according to Emmel, Levinson and Fisch,[333] is six or eight times that of the adult, although the platelet count is the same. Platelet material from the adult and calcium chlorid both reduce the coagulation time, but not as much as the addition of tissue extract which makes the coagulation time the same as the adult. Stephan [334] studies the active and inactivated blood serum and blood plasma of the specimen to be tested with the action of normal serums and plasms; and the effect of normal blood serum and blood plasma of a known value on the coagulation time of the unknown specimen. This gives the pathologic factors. With his method, the coagulation time of normal blood is from twenty-eight to thirty-three minutes.

Corachan and Mones [335] insist on the value of the *warning of the coagulation index* as a pre-operative test. When the coagulation time is slow 3 or 4 grains of calcium chlorid per day, before the operation, may bring the coagulation time up to normal. Petrén [336] tests coagulation of blood in jaundice by the bile-acid-alkali test. Normally from 0.55 to 0.66 per cent. of bile-acid-alkali is necessary to prevent coagulation. If

331. Rodda, F. C.: Am. J. Dis. Child. **19**:269 (April) 1920.
332. King, G., and Murray, H. A.: J. A. M. A. **74**:1452 (May 22) 1920.
333. Emmel, V. E.; Levinson, S. A., and Fisch, M. E.: J. Exper. M. **31**:117 (Feb.) 1920.
334. Stephan, R.: Deutsch. med. Wchnschr. **46**:684 (June 17) 1920.
335. Corachan, M., and Mones, F. G.: Siglo méd., Madrid **66**:935 and 960 (Nov. 1) 1919; Abstr. J. A. M. A. **74**:68 (Jan. 3) 1920.
336. Petrén, G.: Beitr. z. klin. chir. **120**:501, 1920.

from 0.45 to 0.40 per cent. prevents coagulation, there is danger of hemorrhage during or after operation; if 0.30 per cent. prevents hemorrhage, operations are contraindicted.

Kinsella and Brown [337] report a retarded coagulation time and a decrease in the platelet count in influenza.

Szenes [338] finds that after an initial retardation, *irradiation of the spleen* accelerates the coagulation time, doubtless due to the breaking down of lymphocytes in the splenic follicles liberating thromboplastic substances. Jurasz [339] thinks irradiation of the spleen with roentgen rays may prove effective in stopping hemorrhage, and be of value from twelve to fifteen hours before operation in cases in which the coagulation time is lengthened. Stephan [340] has used this method successfully in a case of purpura fulminans.

Mills [341] finds that extract of the lung and kidney, and to a lesser degree extracts of skin, possess a strong coagulative activity. The potency of the lung may be a special protection in pulmonary diseases. Tait [342] thinks that the arrest of hemorrhage is due to the agglutination of certain cells "thigmocytes" which are highly phagocytic and on breaking down exude thrombin. When anticoagulants are added, the thigmocytes (platelets and spindle cells) are unaltered. Foreign surfaces and dirt give surfaces to which the cells may adhere, and become altered. Houssay and Sordelli [343] find that twenty-two venoms, including cobra venom, prevent coagulation by destroying cytozym which normally combines with serozym and calcium to form thrombin, but that lachesis and crotalus venoms have a special coagulating power that coagulates even citrated blood. Menten [344] finds that the anticoagulant power of hirudin and cobra venom is destroyed by an increase in acidity, while with peptone prevention the acidity is always increased, so that the mechanism differs with peptone.

The relationship between *coagulation time in the blood of the newborn and cerebral hemorrhage* becomes increasingly important with the discovery that cerebral hemorrhage is found in more than 50 per cent. of all necropsies on infants dying during the first few days of life. Rodda [345] finds that coagulation time and bleeding time are prolonged from the first to the fifth day of life, with the maximal retardation on

337. Kinsella, R. A., and Brown, G. O.: J. A. M. A. **74**:1070 (April 17) 1920.

338. Szenes, A.: München. med. Wchnschr. **67**:786 (July 2) 1920.

339. Jurasz, A. T.: Zentralbl. f. Chir. **47**:824 (July 3) 1920.

340. Stephan, R.: München. med. Wchnschr. **67**:309 (March 12) 1920.

341. Mills, C. A.: J. Biol. Chem. **40**:425 (Dec.) 1919.

342. Tait, J.: J. Physiol. **53**:19 (Sept. 5) 1919.

343. Houssay, B. A., and Sordelli, A.: Prensa méd. Argentina **6**:113 (Oct. 20) 1919; Abstr. J. A. M. A. **74**:140 (Jan. 10) 1920.

344. Menten, M. L.: J. Biol. Chem. **43**:381 (Sept.) 1920.

345. Rodda, F. C.: J. A. M. A. **75**:452 (Aug. 14) 1920.

the fifth day and a return to normal on the tenth day. The delayed times correspond to the age incident of hemorrhagic disease and cerebral hemorrhage. The coagulation time may be brought back to normal by the subcutaneous injection of blood—which Voncken [346] calls homo-hemotherapy. Foote [347] says that blood coagulation tests should be routine examinations on all newborn infants, and in every case of suspected intracranial hemorrhage substances to increase blood coagulability are indicated.

HEMOPHILIA

Nobecourt [348] says that the most effective treatment for hemophilia at present is horse serum and the subcutaneous injection of peptone solutions. He gives the treatment in detail. It gives marked improvement but is not a cure. After transfusion in Bulger's [349] case of hemophilia, the coagulation time was the same as in the control, but both the coagulation time and the prothrombin time lengthened, but at the end of a month it was still less than before the transfusion. Weil [350] controls his hemophilia cases by subcutaneous injection of 20 c.c. of animal or human blood serum every two months. Of fifty cases treated in fifteen years he has not lost one patient. He regards hemophilia as a congenital functional malformation of the elements in which blood and blood vessels originate. Chalier [351] considers the mother's blood serum the most effectual treatment for congenital hemophilia.[352]

INTRACARDIAL AND INTRAVENOUS INJECTIONS

The controversy concerning the best method for *blood transfusion* is still unsettled, direct and indirect methods having their advocates. Schaaf [353] says that the citrate method is the one of choice, and in pernicious anemia transfusion produces an immediate general improvement, but it has no curative value. Graham [354] says that the ideal method is either direct from artery to vein or indirect from vein to vein without citrate. In pernicious anemia transfusion may cause remissions. The benefit is not necessarily in proportion to the volume of blood received. Terrien,[355] instead of transfusing an infant 13 months

346. Voncken, J.: J. A. M. A. **75**:307 (July 31) 1920.
347. Foote, J. A.: Am. J. Dis. Child. **20**:18 (July) 1920.
348. Nobecourt, P.: Paris méd. **9**:452 (Dec. 6) 1919.
349. Bulger, H. A.: J. Lab. & Clin. M. **6**:102 (Nov.) 1920.
350. Weil, P. E.: Médecine, Paris **1**:354 (March) 1920.
351. Chalier, J.: Rev. de méd. **36**:522 (Sept.-Oct.) 1919.
352. Chalier, J.: Presse méd. **28**:773 (Oct. 30) 1920.
353. Schaaf, F. H. K.: Minnesota Med. **3**:382 (Aug.) 1920.
354. Graham, J. M.: Edinburgh M. J. **24**:282 (May) 1920.
355. Terrien, E.: Bull. et mém. soc. méd. d. hôp. de Par. **43**:1134 (Dec. 26) 1919.

old with malignant measles, injected whole blood subcutaneously with excellent results.

Van Dijk [356] calls attention to the development of malaria in a patient who was given serum from an influenza convalescent. The donor's blood contained no parasites at the time of transfusion although they had been present some months previous. Busman [357] calls attention to the fact new rubber tubing may give a marked reaction when it is used for transfusion. It is rendered harmless by soaking for six hours in normal sodium hydrate solution. Widakowich and Madrid [358] note that agglutination reactions in serum and in plasma differ. Normally, serum agglutinates alien erythrocytes more intensely than plasma, but in syphilitics, plasma agglutinates more than serum, and this is of importance in blood grouping for transfusion into a syphilitic. Kolmer and Matsumoto [359] point out that while all horse serum contains agglutinins for human erythrocytes, intravenous injection of horse serum does not introduce sufficient agglutinins and hemolysins to cause effects referable to intravascular agglutination.

Henschen [360] has succeeded in permanently *resuscitating the heart* after complete arrest by the direct injection of a stimulant. He injects epinephrin and pituitary extract directly into the left ventricle. In four cases the effect was instantaneous, but in only one case was recovery complete and permanent. Henschen thinks this is the only successful case on record. He gives illustrations showing five danger zones to be avoided in intracardial injections. Vogeler [361] injected epinephrin directly into a heart which had ceased to beat, and in half a minute the heart was beating and respiration began, to stop again in about six minutes; a second injection had the same transient effect and the child died. Heydtoff [362] injected epinephrin into the heart in a case in which there was total arrest of the heart for five or six minutes, and the heart began to beat rapidly. Artificial respiration was necessary for a time. This is a second case with recovery.

Aikman [363] discusses the methods for administration of saline and other solutions to children. In intravenous injections, one-sixtieth of the body weight can be introduced. In infants this is best done through

356. Van Dijk, H.: Nederlandsch Tijdschr. v. Geneesk. **2**:1181 (Sept. 25) 1920.

357. Busman, C. J.: J. Lab. & Clin. M. **5**:693 (Aug.) 1920.

358. Widakowich, V., and de Madrid, S.: Semana méd. **27**:296 (Feb. 26) 1920.

359. Kolmer, J. A., and Matsumoto, M.: J. Immunol. **5**:75 (March) 1920.

360. Henschen, K.: Schweiz. med. Wchnschr. **50**:261 (April 1) 1920; Abstr. J. A. M. A. **74**:1610 (June 5) 1920.

361. Vogeler, K.: Deutsch. med. Wchnschr. **46**:740 (July 1) 1920.

362. Heydtoff, E.: Monatschr. f. Geburtsh. u. Gynäk. **51**:318 (May) 1920.

363. Aikman, J.: J. A. M. A. **74**:244 (Jan. 24) 1920.

the fontanel, but with a closed fontanel either the jugular vein or the femoral vein should be used. Wentworth's technic for entering the femoral vein is given in detail. Friedmann [364] is using the drop method for intravenous infusion. When there is increased lacrimal secretion or slight edema of the eyelids, it is a sign that the patient is getting too much fluid.

Pfalz [365] uses glucose injections in heart disease when there is an indication that the heart is not sufficiently nourished. John [366] uses intravenous injection of glucose solutions in pneumonia. None of the sugar appears in the urine and it all seems to be used for nutrition. Richaud [367] points out that sugar solutions are less toxic than saline solutions and as much as a 1,300 c.c. of isotonic glucose, saccharose or lactose solution may be injected into the veins. Sugar tones up the heart and has an antitoxic action. Rathery and Boucheron [368] inject hypertonic sugar solutions (30 per cent. glucose) intravenously to stimulate diuresis in selected cases of nephritis. It is contraindicated in chronic nephritis with "azotemia." Wells and Blankinship [369] use the intravenous injection of hypertonic glucose solutions in influenzal pneumonia. It withdraws fluid from the body tissues to keep the blood isotonic, and the sugar content of the blood becomes normal without any glycosuria. Barthélemy [370] uses intravenous injections of blood plasma and gum solutions. In cases in which blood pressure must be raised and sustained, gum saline solutions are especially indicated. Bayliss [371] says that gum acacia solutions (6 or 7 per cent. in 0.9 per cent. sodium chlorid solution) are capable of replacing lost blood unless the amount lost is more than 75 per cent. of the blood volume. It does not produce anaphylaxis, or hemolysis nor does it agglutinate blood corpuscles in man.

INTRAVENOUS THERAPY IN SHOCK

Bayliss [371] believes shock is due to the absorption of toxic substances produced by injured cells. Dale [372] finds that exhaustion, pain, cold, thirst, hemorrhage, anesthetics and histamin all have been alleged to play a part in shock. Widal, Abrami and Brissaud [373] believe shock

364. Friedmann, M.: Deutsch. Ztschr. f. Chir. **151**:352 (Nov.) 1919.
365. Pfalz, W.: Deutsch. med. Wchnschr. **45**:1181 (Oct. 23) 1919.
366. John, H. J.: Am. J. M. Sc. **160**:542 (Oct.) 1920.
367. Richaud, A.: Paris méd. **10**:53 (July 17) 1920.
368. Rathery, F., and Boucheron, H.: Bull. et mém. Soc. méd. d. hôp. de Par. **44**:61 (Jan. 16) 1920.
369. Wells, C. W., and Blankinship, R. C.: J. A. M. A. **74**:75 (Jan. 10) 1920.
370. Barthélemy, M.: Rev. de Chir. **39**:271, 1920.
371. Bayliss, W. M.: J. Pharmacol. & Exper. Therap. **15**:29 (March) 1920.
372. Dale, H. H.: Brit. J. Exper. Path. **1**:103 (April) 1920.
373. Widal, F.; Abrami, P. and Brissaud, E.: Presse méd. **28**:181 (April 3) 1920.

is anaphylactic in its nature and due to a destruction of colloids. The most recent views on shock are summed up in two editorials in the *Journal of the American Medical Association*.[374] Anything that causes a diminished volume of the blood that is in effective circulation attributable to loss of normal capillary tone, or to morbid permeability of the capillary walls is followed by a shocklike collapse.[375] Gasser, Erlanger and Meek,[376] in a series of studies on secondary shock, find the blood volume decreased in all experimental cases, and in treatment they conclude that the restoration of blood volume through osmotic action from the tissues is more efficacious than injecting the full amount of the fluid. Mann[377] believes that colloid solutions are better than isotonic salt solutions for restoring blood volume but not as good as blood serum.

The most interesting development in intravenous therapy is the use of strongly hypertonic solutions. White and Erlanger[378] point out that strongly hypertonic glucose and gum acacia solutions injected intravenously cause an immediate increase in blood volume. The crystalloids attract the fluids more rapidly, and the colloids tend to hold the fluid in the circulatory system for a longer period of time. The old rules requiring an absolutely isotonic solution for intravenous injection are swept to the winds by the report of Sachs and Belcher[379] who gave 100 c.c. of a saturated solution of sodium chlorid intravenous at the rate of 1 c.c. per minute. The injection was repeated three successive times. This was a case of brain tumor in which the intracranial pressure was too high for a successful operation, and the saline injection reduced this pressure. The fragility of the red blood corpuscles on daily examinations never varied beyond the normal limits.

374. Editorial, J. A. M. A. **75**:247 (July 24) 1920.
375. Editorial, J. A. M. A. **74**:106 (Jan. 10) 1920.
376. Gasser, H. S.; Erlanger, J., and Meek, W. J.: Am. J. Physiol. **50**:31 (Oct.) 1919.
377. Mann, F. C.: Am. J. Physiol. **50**:86 (Oct.) 1919.
378. White, H. L., and Erlanger, J.: Am. J. Physiol. **54**:1 (Nov.) 1920.
379. Sachs, E., and Belcher, G. W.: J. A. M. A. **75**:665 (Sept. 4) 1920.

INDEX TO VOLUME 21

INDEX TO VOLUME 21